UNIVERSITY OF MICHIGAN
OCT 7 1950
MEDICAL LIBRARY

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY OCTOBER 21 1950

TABLE OF CONTENTS

Value of Genetics in Medicine L. S. PENROSE, M.D. 903

Absorption of Vitamin B_{12} in Pernicious Anaemia:

I. Oral Administration Without a Source of Intrinsic Factor C. C. UNGLEY, M.D., F.R.C.P. ..905

II. Oral Administration With Normal Gastric Juice C. C. UNGLEY, M.D., F.R.C.P. 908

III. Failure of Fresh Milk or Concentrated Whey to Function as Castle's Intrinsic Factor or to Potentiate the Action of Orally Administered Vitamin B_{12}
C. C. UNGLEY, M.D., F.R.C.P., and G. A. CHILDS 911

IV. Administration into Buccal Cavity, into Washed Segment of Intestine, or after Partial Sterilization of Bowel C. C. UNGLEY, M.D., F.R.C.P. 915

Acute Intussusception in Childhood
SIR JAMES SPENCE, M.D., F.R.C.P., and DONALD COURT, M.D., M.R.C.P. 920

Activity in Advancing Years MARJORY W. WARREN, M.R.C.S. 921

Use of Intravenous Amphetamine Sulphate in Acute Barbiturate Poisoning
J. D. N. NABARRO, M.D., M.R.C.P. 924

Pregnancy in Rudimentary Horn of Bicornuate Uterus
DOUGLAS LATTO, M.B., M.R.C.O.G., and RICHARD NORMAN, M.R.C.S., D.Obst.R.C.O.G. 926

MEDICAL MEMORANDA

Larval Conjunctivitis. J. S. CONWAY, D.O.M.S. 928
Arteriovenous Fistula Complicating an Amputation Stump. A. NAYLOR, Ch.M., M.Sc., F.R.C.S. 928

REFRESHER COURSE

Treatment of Ulcerative Colitis. G. E. BEAUMONT, D.M., F.R.C.P. 937

GENERAL ARTICLES AND NEWS

Congress of Internal Medicine, Paris, September, 1950 940
PRESENT STATUS OF CORTISONE AND A.C.T.H. 942
EPIDEMIOLOGY SECTION 955
MEDICAL NEWS 956
QUESTIONS AND COMMENTS 959

REVIEWS

Haematology Expands 929
Diagnostic Radiology 929
Actinomycetes 930
Medical Photography 930

OBITUARY

Sir Ernest Graham-Little, M.D., F.R.C.P.; Sir John McIntyre, K.B.E., C.B., M.C., M.B.; S. Roodhouse Gloyne, M.D.; F. K. Kerr, M.C., M.B.; A. W. Brodribb, B.M.; A. E. Struthers, M.B.; D. C. Edington, M.D.; William Lowson, M.B.; Edward Gillespie, M.B., F.R.C.S. 952-4

LEADING ARTICLES

Eugenics and Heredity 931
Vitamin-A Deprivation in Man 932
Absorption of Vitamin B_{12} 933

ANNOTATIONS

Treatment of Neurosyphilis 934
R.S.M. Section of General Practice 935
Anti-calcifying Action of Phytate 935
Inhalation During Dental Extraction ..936
Cardiac Disease and Pregnancy 936

MEDICO-LEGAL

Claims Against Hospitals: A Difference of Law 954

SUPPLEMENT

Central Consultants and Specialists Committee 165
Sixpence Charge for Prescriptions—C.M.S. SALARIES IN EAST AND CENTRAL AFRICA—ADDITIONS TO LIST OF SPECIAL DRUGS—REMUNERATION OF MEDICAL ADMINISTRATIVE OFFICERS OF REGIONAL HOSPITAL BOARDS, MEDICAL SUPERINTENDENTS, AND REGIONAL PSYCHIATRISTS—MATERNITY MEDICAL SERVICES—WHITLEY COUNCILS FOR THE HEALTH SERVICES 166
GENERAL MEDICAL COUNCIL 167
JOINT ANNUAL MEETING, 1951 167
GENERAL MEDICAL SERVICES COMMITTEE 167
CORRESPONDENCE 168

CORRESPONDENCE

Psychology and Science. SIR CYRIL BURT; FREDERICK DILLON, M.D. 943
Distinction Awards. H. B. NORMAN, B.M. 944
Distinction Declined 944
St. Luke's Day. H. CAIGER, F.R.C.S. 944
Child Health and the Future. C. O. STALLYBRASS, M.D.; F. C. NAISH, M.D.; G. S. ROBERTSON, M.D.; N. J. COOK, M.B. 945
Sea-sickness. J. M. PALMER, M.B.; E. HOUGHTON, M.B.; J. C. L. ADAMS, M.B. 946
Rheumatoid Arthritis. R. HARRIS, M.B. 947
Osteoarthritis and Occupation. W. G. WAUGH, F.R.C.S.Ed.; E. FLETCHER, M.D. 948
Students in Prague. A. HERDAN; S. HALL 948
Jaundice and Para-aminosalicylic Acid. G. A. BALLANCE, M.B. 949
Unabsorbed Sutures. E. E. RAWLINGS, M.D. 949
Globin Insulin. G. M. WAUCHOPE, M.D. 949
Vagotomy. N. C. TANNER, F.R.C.S. 950
Foreign-Body in the Rectum. J. C. ROSS, M.Ch.; KENNETH FRASER, M.D. 950
Swimming-baths. S. T. BEGGS, M.D.; G. W. FLEMING, L.R.C.P.Ed. 950
Poliomyelitis. W. P. SWEETNAM, M.D. ..950
Chloralose. A. ELKELES, M.D. 951
Radiology and the Diagnosis of Miliary Tuberculosis. J. E. BANNEN, M.B. 951
Laboratory Animals. MAY RAW, M.B. ..951
Hydrops Foetalis and Rhesus Incompatibility. W. G. MILLS, F.R.C.S. 951
Should Pregnant Women Receive Streptomycin? M. J. GREENBERG, M.B. 952

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4685, WEEKLY, PRICE 2/-

Copyright

REGISTERED AS A NEWSPAPER

Against exhaustion

The energising and therapeutic effect of glucose is available in a most acceptable form in LUCOZADE.

Whereas ordinary glucose preparations may have a sickly and even nauseating effect on the palate, LUCOZADE is remarkably refreshing. Once tasted — it is never refused.

An improved form of glucose therapy

This pleasing characteristic is of the greatest value in treating cases of shock, physical exhaustion and other conditions requiring glucose ingestion.

(Containing Dextrose, Maltose, and Dextrin in solution equivalent to 23% w/v Liquid Glucose B.P.)

LUCOZADE

LUCOZADE LTD., GT. WEST RD., BRENTFORD, MIDDX.

M.17

From single-cell selection to large-scale production

D.C.L. VITAMIN B_1 YEAST

is subjected to the strictest biological and chemical control. The special yeast contains approximately:

Vitamin B_1	300 International Units per gram. (900 micrograms)
Riboflavin	50 micrograms per gram.
Nicotinic Acid	250-350 micrograms per gram
Vitamin B_6 (Pyridoxin)	25-50 micrograms per gram.

(3 D.C.L. Tablets equal 1 gram)

Members of the Medical Profession are invited to write for full particulars and a trial supply.

THE DISTILLERS COMPANY LTD., EDINBURGH

To all who are interested in Iodine—its effects, its uses, its possibilities — the Chilean Iodine Educational Bureau offers information and advice. Reviews of selected aspects of Iodine usage are available, including:

DISINFECTION OF DRINKING WATER
WORLD GOITRE SURVEY
IODINE AND PLANT LIFE
RHEUMATISM AND ARTHRITIS

Every endeavour will be made to meet your requests for information. There is no charge

Chilean Iodine Educational Bureau

10, STONE HOUSE, BISHOPSGATE, LONDON, E.C.2

HÆMODUCTOR

MODEL 'H'

HOSPITAL SUCTION APPARATUS

The model 'H' Hæmoductor has been designed especially for use in the operating theatre. It consists of a twin-cylinder pump driven by a 1/6 h.p. induction motor which produces a vacuum of 60 cm. Hg. An automatic control cuts off the suction to the bottle when the liquid reaches a predetermined level. The capacity of the bottle is 4 pints. A notable feature of this machine is that the motor can be left running while the bottle is being changed. A resetting push button is situated in the centre of the bottle cap.

Illustrated literature will be sent on request

MEDICAL & INDUSTRIAL EQUIPMENT LTD.

Specialists in Anaesthetic Apparatus and Surgical Instruments

12, New Cavendish Street, London, W.1.

Phones: WELbeck 1851 and 1504. Grams: Narcosis Wesdo, London

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 21 1950

VALUE OF GENETICS IN MEDICINE*

BY

L. S. PENROSE, M.D.

Galton Professor of Eugenics, University College, London

A routine procedure which is accepted as part of the correct technique in clinical medicine is the inquiry into family history. The student is instructed to ascertain the state of health or cause of death of the parents, brothers, sisters, and children of the patient. The facts elicited may tell him, it is alleged, whether the patient is disposed by heredity to any particular disease (Hutchison and Hunter, 1949). In spite of these injunctions, the use which is to be made of the family history remains wrapt in obscurity. From the patient's point of view, perhaps this is advantageous.

In the past there has been a tendency to look upon the family history as though it were a kind of Wassermann test, usually negative but occasionally positive and sometimes strongly positive. When the family history reaction turned out to be positive the disease was regarded as hereditary and the patient's condition would be apt to be judged incurable or even unmodifiable. In these circumstances the first thing to be done after taking a family history would be to forget all about it and to treat the case on its own merits. Indeed, the positive or negative family history is a very poor index of heritability. The recurrence of disease of a particular kind in more than one member of a family is no certain index of genetical causation. Serious mistakes were made in the past, rickets, syphilis, leprosy, and tuberculosis being classified as hereditary conditions because they were familial. Conversely, a rare recessive trait or a fresh mutant often appears without any trace of familial incidence.

It is now clear to most physicians that the interaction between hereditary constitution and environment is exceedingly subtle and complex. The course of every ailment known to medicine is influenced to a greater or lesser degree by the genetical structure of the individual patient. We are accustomed to the necessity of making exhaustive researches into environment, both physical and psychological, in order to understand the causes of disease. Infection, diet, occupation, and climate are searched for causal factors.

Similarly, it is logical to investigate the details of genetical constitution as profoundly as possible. We must, however, avoid imagining that genetical inquiry will lead us towards *the* cause of the condition except in the rarest cases. The correct interpretation of pedigree material is usually a matter of the greatest difficulty, partly because of the limited state of our knowledge of human genetics at the present time and partly on account of the inadequacy of the inquiries made at routine examinations—for example, the omission of inquiries about parental consanguinity. My first point is, then, that if family histories are to be taken as part of routine clinical procedure it is surely worth while to teach medical men and women enough of the principles of human genetics to enable them to know what use, if any, is to be made of them.

The central question for discussion is, however, the actual value of genetics in clinical medicine at the present time. It must be freely admitted that this value is very limited, and nothing would be more injurious to the proper development of human genetics than to give the impression that it will prove to be any kind of a panacea.

Use in Serology and Pathological Biochemistry

There are two strictly clinical fields in which genetics has a very definite place. One of these is the study of serology. Incompatibility of donor's corpuscles with recipient's serum has been recognized as an avoidable danger in transfusion if cross-matching of bloods is carried out. Genetical knowledge is helpful here but not absolutely essential. Incompatibility of a foetus with its mother can, however, be predicted on genetical grounds and appropriate treatment planned before examination of the foetal blood is possible. The association of foetal disease with rhesus incompatibility, first recognized by Levine, Katzin, and Burnham (1941), is the most dramatic and convincing demonstration of the use of genetics in clinical medicine.

There is another field in which the value of genetics is becoming increasingly obvious—namely, the study of inborn biochemical specificities. The groundwork of the subject was well prepared by Garrod (1902), who showed that genic differences between individuals, responsible for clinical peculiarities, could be detected biochemically. The first disturbance to be fully described was alkaptonuria, which only very rarely produces any disability. This condition contrasts with phenylketonuria, first described by Fölling (1934), which is invariably associated with a subnormal level of mental functioning. There are conditions of intermediate medical significance, like hyperuricaemia, which are usually innocuous but sometimes cause severe symptoms, like gout.

The successful treatment of some cases of inborn methaemoglobinaemia with ascorbic acid or with methylene blue, and the treatment of cases of the syndrome of de Toni and Fanconi with vitamin D and alkali, have shown that knowledge of pathological biochemistry in these hereditary diseases can lead to striking practical results. The genetical part of the work enables such treatments to be accurately aimed because we know that gene differences produce sharp distinctions. If a precisely defined biochemical diathesis is

*Read in opening a discussion in the Section of Medical Genetics at the Annual Meeting of the British Medical Association, Liverpool, 1950.

detected in a healthy relative of a known case of illness caused by the same genetical peculiarity, prophylactic measures can be confidently recommended. Bacterial genetics have latterly demonstrated that genic differences are often manifested in the loss of particular enzymes. Sometimes, however, genic effects are shown in specific peculiarities of membrane permeability or, as in some anaemias, peculiarities in the structure of the haemoglobin molecule. These discoveries, together with the advances of human biochemical genetics, have enabled the study of diathesis to be placed on a sound and logical basis, and great progress in this field may now be expected.

Eugenics in Prevention of Hereditary Disease

I now come to the negative side of the question—namely, the prevention of hereditary disease by eugenic recommendations. A view sometimes expressed is that it should be part of any efficient scheme of public health to attempt to cleanse the population of injurious genes. Such an aim, directed not towards improving the health of the existing population but that of future generations, is hardly consistent with the fundamental medical tradition of treating every individual case on its own merits. In the present state of genetical knowledge, moreover, the prospects of making any appreciable change in the genetical composition of the population by preventive eugenics are remote. Evidence is accumulating which suggests that natural selection has produced balanced genetical systems that are resistant to change, and I have attempted to apply the idea to the genetics of intelligence (Penrose, 1950).

Benefits for individual parents or prospective parents can be derived from genetical studies on rare familial diseases. If unaffected carriers of injurious genes could be diagnosed much comfort could be given to inquiring patients. Little practical help can be expected from genetical prognoses in relation to common diseases—for example, those with a frequency of the order of 1 in 100 or commoner. The belief was held by earlier workers, and is still accepted in some quarters, that many common traits, such as mental defect (Goddard, 1914), diabetes (Pincus and White, 1933), and schizophrenia (Kallmann, 1938) are inherited in simple ways, perhaps caused by common recessive genes. A careful study of the natural histories of these conditions, as exemplified in variability of clinical type, onset age, and sex incidence, at once rules out all simple genetical explanations. Furthermore, the elements in the causation due to environment can be changed but constitution cannot, so that medicine must concentrate on environment.

Besides strictly genetical problems arising in medicine, there are many of a semi-genetical kind concerned with the maternal influences on foetal development. These influences may be closely associated with maternal age, parity, health, nutrition, and so on. Advice is often requested by prospective parents on all these matters, and it might be advantageous if full use could be made in health services of the rather limited knowledge at present available.

Need for Accurate Information

Though human geneticists hope ultimately to be of practical use, at present they are contributing to the general body of scientific knowledge rather than to therapeutic medicine directly. While genetics has some contribution to make to medicine, this is far outweighed by the service which has been and will continue to be rendered by medicine to genetics. One may ask, then, what is particularly required from medical science at the present time? The question is easy to answer. Accurate information is needed about the incidence of disease in the general population. The ascertainment of really useful data on these matters is difficult. The geneticist requires to know not only the crude incidence of a condition like, say, diabetes mellitus, but the incidence in different age groups as well, classified also by sex. Moreover, degrees of severity have to be taken into account. The classification into two categories of presence and absence of disease is insufficient, because there are usually many degrees of severity.

The importance of such data in medical genetics is clearly seen in the model investigation of Doll and Buch (1950) on the familial incidence of gastric and duodenal ulcer. A population survey previously carried out gave much greater stability to their results than could have been provided even by careful analysis of a control series of families. Precise knowledge of population data is also necessary for the estimation of gene frequencies, of mutation rates, and of fertility or biological fitness of particular genotypes. Beyond this, it is essential in the study of sex influence, begun by Sedgwick (1861), and of genetical and environmental modifying agencies. Without such data the meaning of consanguinity cannot be assessed (Harris, 1949). From the point of view of future work on the genetics of relatively common conditions like cancer, diabetes, cardiovascular disease, schizophrenia, rheumatism, and so on, the ascertainment of the incidence among the population should, in my view, take precedence. Such a task might naturally be included in a programme of social medicine.

With relatively rare abnormalities the measurement of incidence is equally important. Nothing is so misleading to the geneticist as the exclusive recording in medical literature of noteworthy familial cases, neglecting sporadic or "non-familial" examples, which are usually more characteristic of the conditions concerned. Let me give an example. From time to time cases of mongolism in two sibs—two cousins or other close relatives—are reported in the literature. How do we know whether these instances imply real familial concentration? If cases were distributed at random sooner or later two would occur in the same family. Moreover, since maternal age affects the incidence of mongolism, in that young mothers are much less prone to have such offspring than older mothers, two related cases with maternal ages between, say, 20 and 30 years are much more remarkable (about twenty-five-fold) than two cases with maternal ages over 40 years.

Similar problems arise with most familial studies because in so many diseases the ages of onset are subject to wide variation. Such an example is mammary cancer. Familial cases in females aged 60 or over will often occur even if there is no hereditary influence. The population incidence, ascertainable in mortality statistics at all ages, however, enables a base-line to be drawn for examining the strength of any familial tendency there may be in this condition. It is clear from the case material collected by the Galton Laboratory staff, as well as from that collected at the Royal Cancer Hospital, that relatives of sufferers from mammary cancer are significantly more prone to the same disease than are random members of the general population; such relatives are, however, not more than normally predisposed to develop cancer at other sites (Penrose, MacKenzie, and Karn, 1948).

Summary

To summarize, then, the family history is accepted as an integral part of clinical examination. It should be properly taken and its uses and limitations appreciated. Genetical knowledge has helped treatment directly in the fields of serology and pathological chemistry. It is not likely that harmful genes will be eliminated or even appreciably reduced by eugenical measures, but some guidance can be given to parents in special cases.

Closer contact between geneticists and medical students is desirable if full advantage is to be taken of existing knowledge. Even more important is the assistance that properly directed researches in social and clinical medicine could give to the future development of human genetics. At the present time the most pressing need is the ascertainment of population frequencies of any diseases determined, to a significant degree, by genetical factors. Such ascertainment would enable the analysis of pedigree studies to be put upon a firm basis.

References

Doll, R., and Buch, J. (1950). *Ann. Eugen.*, **15**, 135.
Fölling, A. (1934). *Hoppe-Seyl. Z.*, **227**, 169.
Garrod, A. E. (1902). *Lancet*, **2**, 1616.
Goddard, H. H. (1914). *Feeble-mindedness: Its Causes and Consequences.* Macmillan, New York.
Harris, H. (1949). *Ann. Eugen.*, **14**, 293.
Hutchison, R., and Hunter, D. (1949). *Clinical Methods*, 12th ed. Cassell, London.
Kallmann, F. J. (1938). *The Genetics of Schizophrenia.* Augustin, New York.
Levine, P., Katzin, E. M., and Burnham, L. (1941). *J. Amer. med. Ass.*, **116**, 825.
Penrose, L. S. (1950). *Brit. J. Psychol.* (General Sect.), **40**, 128.
—— MacKenzie, Helen J., and Karn, Mary N. (1948). *Ann. Eugen.*, **14**, 234.
Pincus, G., and White, P. (1933). *Amer. J. med. Sci.*, **186**, 1.
Sedgwick, W. (1861). *Brit. Foreign med.-chir. Rev.*, **27**, 477; **28**, 198.

ABSORPTION OF VITAMIN B_{12} IN PERNICIOUS ANAEMIA

I. ORAL ADMINISTRATION WITHOUT A SOURCE OF INTRINSIC FACTOR

BY

C. C. UNGLEY, M.D., F.R.C.P.

Physician, Royal Victoria Infirmary, Newcastle-upon-Tyne

There are many who find difficulty in orientating recent work on vitamin B_{12} with teaching based on Castle's original hypothesis. Following experiments in which beef and gastric juice were fed separately and together to patients with pernicious anaemia, it was suggested that an intrinsic (gastric) factor interacted with an extrinsic (food) factor to produce the anti-pernicious-anaemia factor stored in liver. Efforts to obtain from mixtures of beef and gastric juice a product as heat-stable as the liver active principle were, however, unsuccessful. Moreover, the hypothesis failed to explain why the dosage required for orally administered liver extract so vastly exceeded the amount needed for injection. Even when it was shown that the simultaneous administration of a source of intrinsic factor allowed a greatly reduced oral dose of liver (Reimann and Fritsch, 1934) or liver extract (Fouts, Helmer, and Zerfas, 1935) most of us misinterpreted this to mean that liver contained extrinsic factor in addition to liver active principle.

The problem has been clarified by the behaviour of vitamin B_{12}. This heat-stable substance isolated from liver is effective both in pernicious anaemia (West, 1948) and in subacute combined degeneration of the cord (Berk, Denny-Brown, Finland, and Castle, 1948; Ungley, 1949b). It thus fulfils all the criteria of a true "liver active principle."

When administered orally, however, vitamin B_{12} behaves like Castle's extrinsic factor in that small amounts are effective only if accompanied by a source of intrinsic factor (Berk, Castle, Welch, Heinle, Anker, and Epstein, 1948). In this case at least "extrinsic factor" appears to be identical with "liver active principle," interaction with intrinsic factor being necessary only if the material is given by mouth.

The present work is an attempt (*a*) to determine how effectively vitamin B_{12} is absorbed when given alone or with gastric juice, and (*b*) to answer the question: Does Castle's intrinsic factor directly facilitate the absorption of B_{12} or merely protect it from destruction in the gastro-intestinal tract?

The results are described in consecutive papers, with the following subtitles: I. Oral administration without a source of intrinsic factor. II. Oral administration with normal gastric juice. III. Failure of fresh milk or whey concentrate to function as Castle's intrinsic factor or to potentiate the action of orally administered vitamin B_{12} (with Mr. G. A. Childs). IV. Administration into the buccal cavity, into a washed segment of intestine, or after partial sterilization of the bowel. No. V, on the influence of gastric and intestinal juice on the availability of vitamin B_{12} determined microbiologically (with Dr. W. F. J. Cuthbertson), will be published later.

To facilitate cross-reference, the cases are numbered from 101 in Paper I, 201 in Paper II, and so on.

Methods

Haematological methods, dietary control, and selection of cases have been described (Ungley, 1949a). All patients had pernicious anaemia with megaloblastic marrow and complete achlorhydria even after histamine and alcohol. All showed at least one characteristic reticulocyte response to potent material and ultimately attained complete remission, usually after further treatment with vitamin B_{12} or liver extract. Only relevant parts of the case histories are included.

Dietary histories are summarized because of the possibility—still being explored—that even in pernicious anaemia the chance of a patient responding to orally administered vitamin B_{12} may be greater if low intake as well as deficient absorption had contributed to the development of deficiency; and because deficiency of other dietary factors such as folic acid could interfere with the response to vitamin B_{12} even if the latter were injected parenterally.

Pure vitamin B_{12} was used except in the first period of Case 101, in which vitamin B_{12a} was given, and in five cases receiving 3,000 μg. as concentrate, to be reported fully later.

The time of administration was considered in relation to the phases of digestion and the nature of foods ingested within six hours which might affect the availability of vitamin B_{12} to bacteria or to the host. The large doses of vitamin B_{12} concentrate ($\equiv$3,000 μg.) were given fasting, and no food was ingested until six hours afterwards.

Responses were assessed on the increase of red blood cells in 15 days rather than on the reticulocytosis, although the latter sometimes afforded valuable confirmation. Haemoglobin and packed-cell volume were recorded as a further check. The double reticulocyte response method of Minot and Castle (1935) was used in some cases.

To facilitate comparison and to avoid the need for ambiguous terms such as "good," "maximal," or "optimal" response, the increase of red blood cells in 15 days was expressed as equivalent to the reponse expected from a single injection of so many micrograms of vitamin B_{12} (Ungley, 1949a, Tables II and V). Oral preparations were sometimes given daily, whereas standards for parenteral therapy are based on the response to a single dose. Nevertheless the total amount could be compared with the parenteral dose which would be expected to give the same response (see Table). When subsequent tests showed that the patient's actual responsiveness to injected material was below expectation the oral-dose/injection-dose ratio was corrected accordingly.

Even the "corrected" ratios are very approximate. The expected rise of red blood cells in 15 days from a given dose (between 5 and 80 μg.) of injected material has a standard

deviation of 300,000 per c.mm. The sources of deviation are partly technical and partly individual variations in response. Similar deviations in the observed response to oral therapy—and they might be greater—could produce wide and not necessarily linear variations in the parenteral dose which would be expected to produce an equivalent response. This means that the results of any single experiment can give only a rough indication of the oral-dose/parenteral-dose ratio.

Results

Daily doses of 5 μg. were ineffective in Case 201 (see Paper II).

Daily doses of 80 μg.* had a slight effect in the following case.

Case 101

A woman aged 59 had pernicious anaemia without neurological involvement. The dietary history was satisfactory except that she took no cheese and little milk. After a satisfactory control period of 13 days red blood cells numbered 1,700,000 per c.mm., haemoglobin 6.2 g. per 100 ml., reticulocytes 1%, M.C.V. 128 μ^3, M.C.H. 36.7 μμg., M.C.H.C. 30.3%, white blood cells 2,400 per c.mm. The marrow was megaloblastic.

First and Second Periods.—The daily oral administration of 80 μg. of vitamin B_{12o} (Lester Smith, 1950; Ungley, 1950) led to a reticulocytosis, beginning on the third day and reaching 8.8% on the ninth day, and to a small rise of red blood cells. Substituting pure vitamin B_{12} for vitamin B_{12o} led to a secondary reticulocytosis of 7.2% on the seventh day but no further increase of red blood cells.

	First Period			Second Period			Third Period	
Days:	0	5	10	14	19	24	29	34
R.B.C. (mills./c.mm.)	1·70	1·80	1·92	2·21	1·98	2·14	2·45	3·07
Hb (g./100 ml.) ..	6·2	6·8	7·1	8·0	7·6	8·3	8·9	10·5
P.C.V. %	21·0	—	22·0	23·0	22·5	25·0	28·0	—

In the *third period* 1 μg. of vitamin B_{12} was injected daily. Reticulocytes did not exceed 3%, but red blood cells increased rapidly.

Comment.—The reticulocyte responses in the first and second periods point to some therapeutic effect from orally administered material, although equally definite responses have been observed after single injections of only 2.5 μg. Moreover, the increase in red blood cells in 24 days after a total quantity of 1,920 μg. (Fig. 1) was not significantly greater than would have been expected in 15 days from a single injection of 2.5 μg. (Ungley, 1949a, Table V). In other words, the apparent oral-dose/injection-dose ratio was several hundreds to one. The increase of red blood

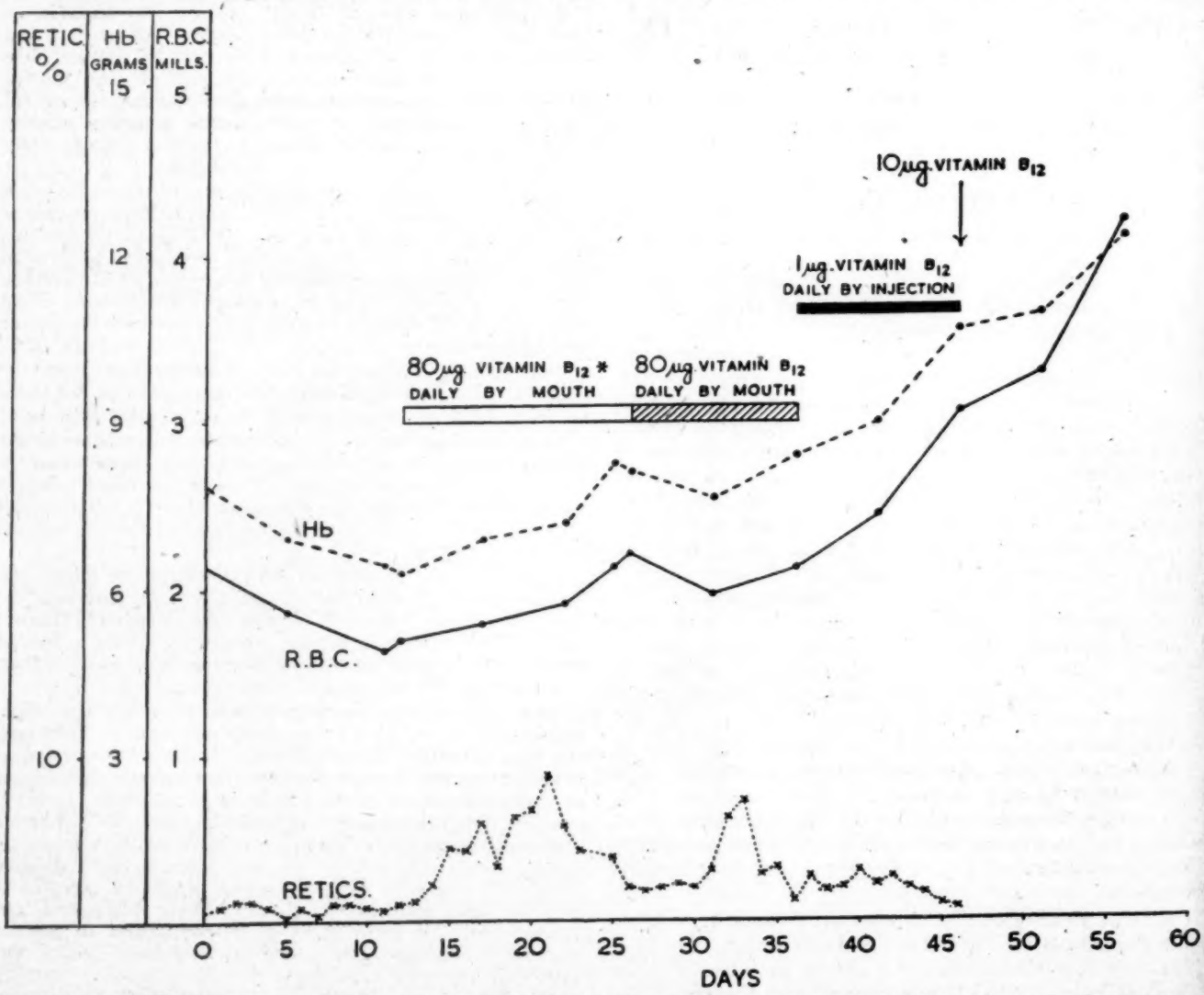


FIG. 1.—Case 101. Showing poor response to total of 1,920 μg. of red crystalline material by mouth followed by a normal response to daily injections of 1 μg.

*The variety of vitamin B_{12} used in the first period was vitamin B_{12o}.

Results Obtained by Various Workers

Author	Case	Haemopoietic Response				Oral Therapy B_{12} (μg.)	Apparent Ratio		Correction Based on Responsiveness to Injected B_{12}		Corrected Ratio		Presumed Absorption	
		E_0	Retic. Peak	I_{10}	I_{15}		Total Dose Given (μg.)	Parenteral Dose : Expected to Give Similar Response (μg.)	Dose Injected (μg.)	Dose Expected to Give Similar Response (μg.)	Oral Dose	Parenteral Dose	Per Dose (μg.)	%
Berk *et al.*	101	1·56	5·7	0·35	—	5×10	50	: Less than 2·5	No record				Less than 0·25*/5	Less than 5*
Ungley ..	201	1·40	Nil	Nil	—	5×10	50	: Nil	40‡	: 5	—		Nil/5	Nil
Hall *et al.*	Fig. 3	1·50‖	5·9	Nil	Nil	5×7	35	: Possibly 1·25	13×5 =65‡	: 80	Possibly 30	: 1	Less than 0·2/5	?3 or 4
,,	Fig. 1	1·75‖	Nil	Nil	—	25	25	: Nil	25	: 5	—		Nil/25	Nil
Spies *et al.*	2	2·24	Nil	Nil	—	30	30	: Nil	25	: 5	—		Nil/30	Nil
,,	2	1·99	Nil	Nil	—	50	50	: Nil					Nil/50	Nil
,,	3	2·70	2·6	Negligible	—	100	100	: ?Nil	45	: Less than 5	—		Nil/100	Nil
,,	3	2·70	2·0		—	400	400	: Nil					Nil/400	Nil
Campbell *et al.*	—	No record	"Submaximal response"			75	75	: ?	No record		—		Some*/75	Some*
,,	—	,,	"Failed to respond"			1,000	1,000	: Nil	,,	,,	—		Nil*/1,000	Nil*
West ..	—	,,	"Maximal reticulocyte response"			600	600	: ?	,,	,,	—		Some*/600	Some*
Spies *et al.*	2	1·28	21·0	—	1·40†	800×2 =1,600	1,600	: 20	25	: 5	16	: 1	50/800	6
,,	1	2·27	35·7	—	1·04‖	450×10 =4,500	4,500	: 10	Said to have had similar response to 75 μg.		Doubtful		1*/450	0·2*
Ungley ..	101	1·70	8·8	—	0·44 in 24 days	80×24 =1,920	1,920	: More than 2·5	10×1 =10	: 10	Several hundred	: 1	0·1 or 0·2/80	Less than 0·3
,, ..	102	1·52	32·8	—	2·30	3,000	3,000	: Much over 160§	R.B.C. level too high		—		Much over 160*/3,000	5 or 10*
,, ..	103	1·67	26·8		2·00	3,000	3,000	: 160§	,,	,, ,, ,,	—		160*/3,000	5*
,, ..	104	1·80	24·6		1·72	3,000	3,000	: 80	,,	,, ,, ,,	—		80*/3,000	2 or 3*
,, ..	105	2·56	26·0		1·75	3,000	3,000	: Nearly 160§	,,	,, ,, ,,	—		Nearly 160*/3,000	5*
,, ..	106	1·91	29·6		1·72	3,000	3,000	: 80	,,	,, ,, ,,	—		80*/3,000	2 or 3*

E_0 = Initial erythrocyte count. I_{10} = Increase of erythrocytes in 10 days. I_{15} = Increase of erythrocytes in 15 days.

‖ From chart. † Calculated from I_{10}. ‡ Some of the response may have been due to previous therapy. § These are the calculated equivalents, but the dose-response curve for injected B_{12} has not yet been carried beyond 160 μg. and must flatten out sooner or later. It follows that the amounts of B_{12} actually absorbed may have been greater than those indicated in the table. * Ratios and absorption figures thus marked are uncorrected because the actual response to parenteral therapy was not observed. "Nil" = Response not measurable, but some vitamin B_{12} may have been absorbed.

cells after 10 daily injections of 1 μg. was equivalent to the rise expected from a single dose of 10 μg. Some of this increase may have been due to therapy in the preceding period, but at least there is no suggestion of "resistance" to vitamin B_{12}, and the question of correcting the ratio does not arise.

Five Other Cases

Five patients (Cases 102–106) have recently been given orally a single dose of 3,000 μg. as a concentrate. The cases are the first of a new series, and a full report will be published later. The reticulocyte response was maximal in all, and the increase of red blood cells in 15 days was equivalent to that which would have been expected from single injections of 80 μg., 80 μg., nearly 160 μg., 160 μg., and much over 160 (? 320) μg. The apparent oral-dose/parenteral-dose ratio was between 10 and 40 : 1. The red cell levels reached were so high that comparative tests with parenterally administered vitamin B_{12} were impracticable, but these large responses are perhaps enough to indicate that the patients were not resistant to vitamin B_{12} (see Table).

Indeed, these responses are as great as any observed with injected vitamin B_{12}, which has not been tested in doses over 160 μg. Up to this level there was still a straight-line relationship between mean response and logarithm of dose. Sooner or later the dose-response curve presumably flattens out—i.e., there comes a point beyond which any further increase in dose makes no difference to the rise of red blood cells in 15 days. If 160 μg. is this upper

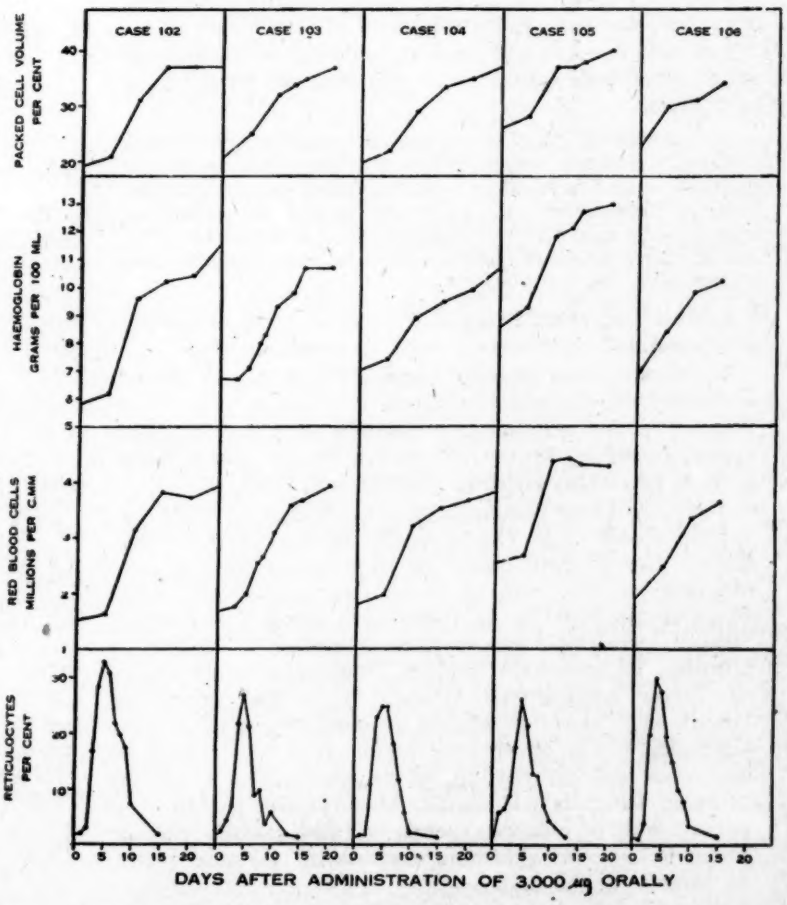


FIG. 2.—Effect in five cases of a single dose of 3,000 μg. of vitamin B_{12} as a concentrate.

limit—and it may vary from case to case—then the figures marked (§) in the Table may be too low.

Discussion

The Table includes results obtained by other workers, whose names will not necessarily be repeated in the text. Daily doses of 5 μg. produced either no response or a small reticulocytosis without rise of red blood cells. In addition to the cases in the Table, Castle (private communication, 1950) has observed 10 others, in six of which there were detectable reticulocyte responses as follows:

Initial R.B.C. in mills./c.mm.	2·25	1·25	1·65	1·60	1·58	1·55
Reticulocytes %	4·3	3·1	14·1	4·0	2·7	11·3

Although not included in the Table, some cases from other sections are worth mentioning here. Negative or trivial responses were observed in two patients receiving daily doses of 10 μg. vitamin B_{12} with fresh milk and in three others given a single or split dose of 50 μg. with whey concentrate (Paper III). A single dose of 80 μg. was ineffective in Case 404 (Paper IV).

In reported cases single doses of 25, 30, 50, 100, 400, and 1,000 μg. gave either negative or trivial results.

In one patient 75 μg. gave a "suboptimal response" and another showed a "maximal reticulocyte response" to 600 μg., but the authors do not give details.

A response to two doses of 800 μg. as concentrate was about equal to the response expected from 20 μg. by injection. The patient, however, was relatively unresponsive to injected vitamin B_{12}—25 μg. gave slightly less than the response expected from 5 μg. Thus the true oral-dose/injection-dose ratio may have been 16 : 1 rather than 80 : 1.

Ten daily doses of 450 μg. were followed by an increase of red blood cells equivalent to that expected from 10 μg. by injection.

An injection of 75 μg. in this patient is said to have given a "similar" response, which if literally true would suggest a response equivalent to 10 μg. Such a degree of unresponsiveness or "resistance" (7.5:1) would reduce the oral-dose/injection-dose ratio from an apparent 450:1 to a possible 60:1, but of course a valid correction cannot be made without fuller information.

In Case 101, given 80 μg. daily, the corrected oral-dose/parenteral-dose ratio was several hundreds to one.

Up to this point one had supposed that the occasional and usually rather poor responses were due to interaction between orally administered vitamin B_{12} and intrinsic factor, traces of which may persist in the gastric juice even in pernicious anaemia (Goldhamer, 1936).

The remarkable responses to a single dose of 3,000 μg. in five recent cases cannot easily be explained on this basis. The patients appear to have effectively absorbed amounts ranging from 80 to 160 μg. or possibly more. From results reported in Paper II it seems that at least 500 ml. of *normal* gastric juice is needed to ensure an adequate haemopoietic response from even 50 to 80 μg. of orally administered vitamin B_{12}. The equivalent volume in terms of pernicious anaemia gastric juice, even supposing traces of intrinsic factor to persist, would be enormous and far beyond the secretory capacity of the atrophic stomach. It would be surprising indeed if a patient with pernicious anaemia secreted enough intrinsic factor to combine with more than one or two micrograms, however large the dose.

These findings suggest that some vitamin B_{12} *can* be absorbed—not efficiently perhaps, but in quite considerable amounts if the dose is large enough—without first combining with the intrinsic factor.

Further speculation seems unjustified, since we do not yet know whether Castle's intrinsic factor combines stochiometrically with vitamin B_{12} or whether it acts as a catalyst. It will be interesting to determine whether a single large dose of vitamin B_{12} administered orally is more or less effective than the same amount of material given in divided doses.

Summary and Conclusions

The absorption of vitamin B_{12} was studied by comparing the effective oral dose with the parenteral dose expected to produce a similar increase of red blood cells in 15 days. The apparent oral-dose/parenteral-dose ratio was corrected if the observed response to injected material was below expectation, indicating a relative resistance to vitamin B_{12}.

In one case daily doses of 5 μg. gave no response. In another, even 80 μg. a day for 24 days produced an increase in red blood cells no greater than would have been expected in 15 days from the injection of 2.5 μg. The response to injected material was normal, so that the corrected oral-dose/parenteral-dose ratio was several hundreds to one. By contrast the oral-dose/parenteral-dose ratio in five cases given a single dose of 3,000 μg. was from 20 to 40 : 1, the increase of red blood cells in 15 days being so great as to suggest the absorption of 80 to 160 μg. or even more. Presumably very little of the vitamin absorbed can have interacted with Castle's intrinsic factor, considering the low quality and quantity of the secretion of the stomach in pernicious anaemia.

Further tests are necessary to determine whether in fact more vitamin B_{12} is absorbed after a single large dose than after the same quantity of material given in divided doses daily.

II. ORAL ADMINISTRATION WITH NORMAL GASTRIC JUICE

BY

C. C. UNGLEY, M.D., F.R.C.P.

Physician, Royal Victoria Infirmary, Newcastle-upon-Tyne

In the preceding paper it was shown that vitamin B_{12} administered orally without a source of intrinsic factor was not efficiently absorbed, although remarkable effects could be obtained with an enormous single dose. The present study attempts to answer two questions: How effectively is vitamin B_{12} absorbed when given with gastric juice? How much gastric juice is needed per microgram of vitamin B_{12}?

Methods

A general account of methods is given in Paper I. Normal human gastric juice was obtained almost entirely from students in response to two injections of 0.5 mg. of histamine at intervals of 30 minutes. Specimens without free HCl and those containing more than a trace of bile were discarded. After filtering through nainsook to remove mucus and debris, the juice was pooled and kept at approximately 5° C. The period of storage did not exceed three days, except in Case 404 (Paper IV), in which the juice had been stored 14 days.

The highly acid juice (*p*H 1 approx.) was neutralized to *p*H 7 with a predetermined quantity of N/1 NaOH. Vitamin B_{12} was then added. In Cases 201, 202, 401, and 402 the mixture was given within two hours, while in Cases 303, 304, 305, and 404 the interval was prolonged to six hours. The mixture was incubated for one hour in Case 304, but not in others. Food was withheld for four hours before and after the mixture. In Cases 303, 304, and 305 the intervals were prolonged to eight hours.

The gastric juice used for the second period of Case 201 was passed through a Seitz filter while still acid. As the Seitz-filtered juice was inactive this procedure was not used again.

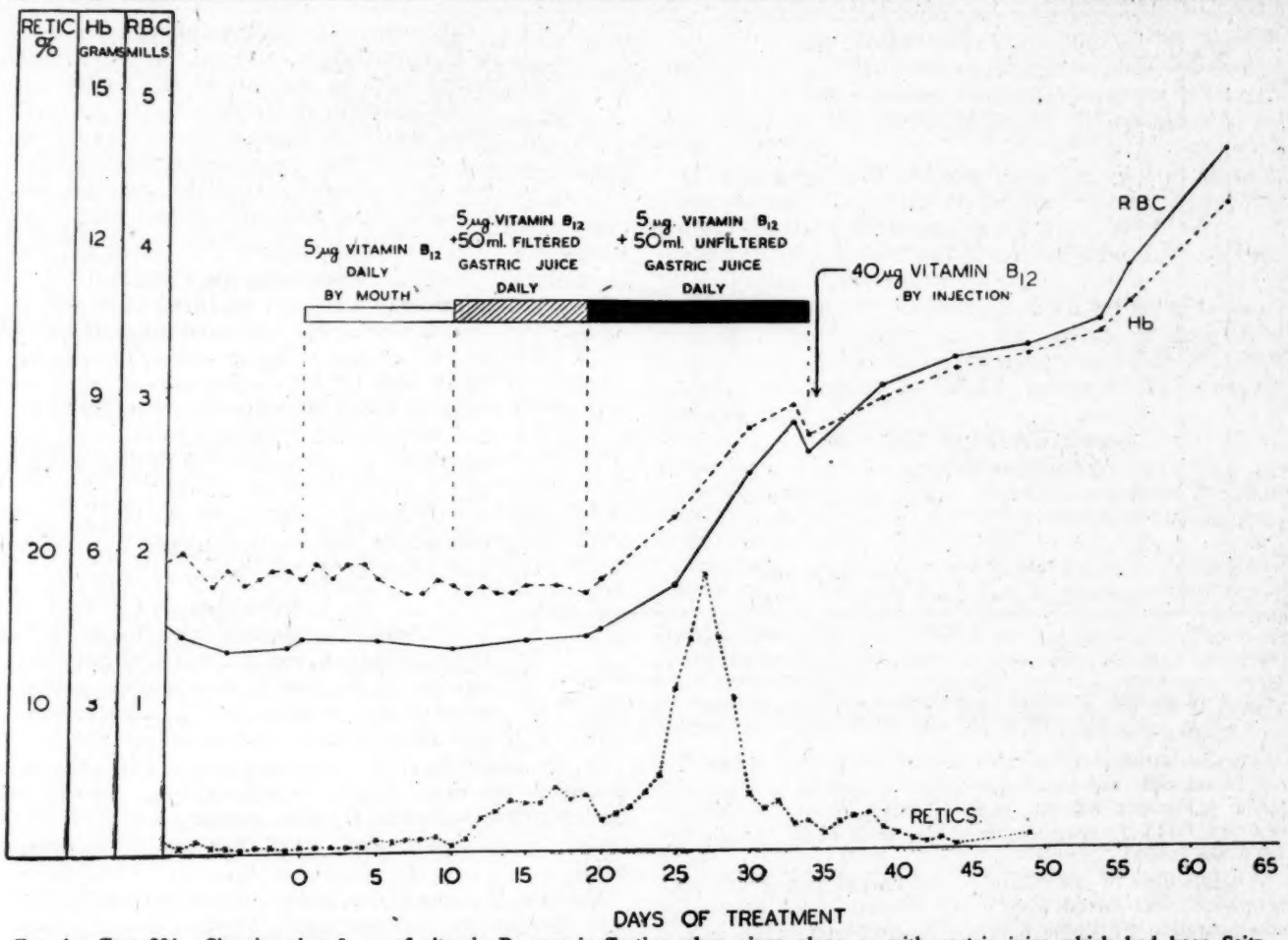

RETIC %
Hb GRAMS
RBC MILLS
5 μg VITAMIN B12 DAILY BY MOUTH
5 μg VITAMIN B12 +50 ml. FILTERED GASTRIC JUICE DAILY
5 μg VITAMIN B12 + 50 ml. UNFILTERED GASTRIC JUICE DAILY
40 μg VITAMIN B12 BY INJECTION
RBC
Hb
RETICS.
DAYS OF TREATMENT

FIG. 1.—Case 201. Showing that 5 μg. of vitamin B_{12} was ineffective when given alone or with gastric juice which had been Seitz-filtered, but produced a good response when given with unfiltered gastric juice.

Results

Eight patients were treated with vitamin B_{12} and normal human gastric juice.

Case 201

A miner aged 58 had pernicious anaemia without neurological involvement. Having recently lost his teeth, he ate little meat, but otherwise his diet was satisfactory.

After 10 days' control period, during which reticulocytes remained less than 1%, the red blood cells numbered 1,400,000 per c.mm., with haemoglobin 5.3 g. per 100 ml., reticulocytes 0.4%, M.C.V. 130.6 μ^3, M.C.H. 38.2 $\mu\mu$g., M.C.H.C. 31.3%, white blood cells 1,700 per c.mm. The marrow was megaloblastic.

In the first period 5 μg. of vitamin B_{12} was given daily by mouth. There was neither reticulocytosis nor increase of red blood cells (Fig. 1).

	←First Period→		←Second Period→		
Days:	0	5	10	15	19
R.B.C. (mills./c.mm.)	1·40	1·38	1·33	1·39	1·41
Hb (g./100 ml.)	5·3	5·3	5·2	5·2	5·0
P.C.V. (%)	17·5	18·6	17·0	—	—

In the second period the same amount of vitamin B_{12} was mixed with 50 ml. of normal gastric juice neutralized just before administration. Before neutralization the gastric juice had been passed through a Seitz filter. Reticulocytes rose to only 4.2% on the seventh day and red cells did not increase.

In the third period the same amounts of vitamin B_{12} and gastric juice were administered, but this time the gastric juice was *not* Seitz-filtered. Reticulocytes rose on the fourth day and reached 18.2% on the eighth day. There was subjective improvement and red cells increased.

	←Third Period→			←Fourth Period→			
Days:	0	6	11	15	20	25	30
R.B.C. (mills./c.mm.)	1·41	1·75	2·48	2·63	3·09	3·28	3·36
Hb (g./100 ml.) ..	5·0	6·5	8·3	8·1	8·9	9·5	9·8
P.C.V. (%)	—	21·0	27·0	28·0	33·0	33·0	35·0

In the fourth period an injection of 40 μg. of vitamin B_{12} led to a negligible reticulocytosis of 2.4% on the fourth day. Red blood cells continued to increase.

Comment.—The daily oral administration of 5 μg. of vitamin B_{12} alone or with Seitz-filtered gastric juice was ineffective. The same quantity with unfiltered gastric juice was effective. The increase of erythrocytes in 15 days after giving a total of 75 μg. with unfiltered gastric juice was equivalent to the response expected from an injection of 10 μg. In fact, however, the patient was relatively "resistant" to injected material in that the increase of red blood cells after 40 μg. was slightly less than that expected from 5 μg. Even then some of the increase may have been due to previous therapy. Correction for this resistance reduces the oral-dose/parenteral-dose ratio from an apparent 7.5 : 1 to the region of unity.

Case 202.—Administration of 50 μg. Vitamin B_{12} with 500 ml. of Gastric Juice by Stomach Tube

A woman aged 63 had pernicious anaemia with sore smooth tongue and minor neurological involvement. The dietary history was normal.

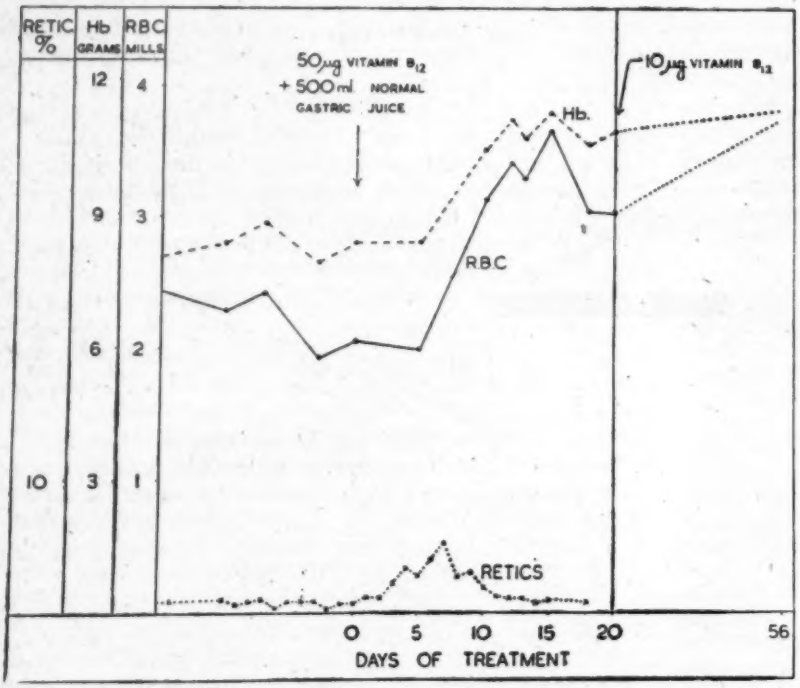


FIG. 2.—Case 202. Response to single dose of 50 μg. of vitamin B_{12} with 500 ml. of normal gastric juice given by stomach tube.

After a satisfactory control period of several weeks the red blood cells numbered 2,050,000 per c.mm., with haemoglobin 8.3 g. per 100 ml., M.C.H., 40.4 μμg., M.C.V. 127 μ^3, M.C.H.C. 31.9%, reticulocytes 0.6%, and white blood cells 4,400 per c.mm.

A single dose of 500 ml. of pooled normal gastric juice was neutralized and mixed with 50 μg. of vitamin B_{12} just before administration by stomach tube. Reticulocytes began to rise on the fourth day, reaching 5.2% on the seventh day (Fig. 2).

Red blood cells increased rapidly, sore tongue was relieved, appetite and well-being were restored. These effects lasted fully 15 days, but by the twentieth day the tongue was again sore and the counts were beginning to fall. Injections of vitamin B_{12} subsequently brought about complete remission.

Days:	0	5	10	15	20
R.B.C. (mills./c.mm.)	2·05	1·99	3·13	3·66	3·02
Hb (g./100 ml.)	8·3	8·3	10·4	11·3	10·8
P.C.V. (%)	26·0	27·0	35·0	37·0	31·5

Comment.—The increase of red blood cells in 15 days slightly exceeded the response expected from an injection of 40 μg. Because of this excellent result there can be no doubt about the patient's responsiveness to vitamin B_{12}, even though the actual effect of injection was not measured. Thus the apparent oral-dose/parenteral-dose ratio of near unity needs no correction for " resistance " to vitamin B_{12}.

Remaining Six Cases

These six cases are described in Papers III and IV. Case 401 was given 5 μg. daily with 50 ml. of gastric juice. Case 402 received 40 μg. with 150 ml. of gastric juice. Case 404 received 80 μg. with 500 ml. Cases 303, 304, and 305 received 50 μg. and 500 ml. of gastric juice after a preliminary trial of milk or whey as a source of intrinsic factor.

The findings in the eight patients are summarized in the accompanying Table along with other published cases.

Discussion

Differences in dietary control and in the source, filtration, storage, and time of administration of the gastric juice may account for some of the variation in the results observed (see Hall, Morgan, and Campbell, 1949).

In the first period of treatment in three of the cases described by Berk, Castle, Welch, Heinle, Anker, and Epstein (1948), vitamin B_{12} and gastric juice were given twelve hours apart and there was no haemopoietic effect.

Vitamin B_{12} given two hours before the gastric juice was effective in one case (Hall, Morgan, and Campbell, 1949). In all other cases cited in the Table the gastric juice and vitamin B_{12} were given simultaneously.

In the cases of Berk *et al.* and in mine, the diet was restricted and no food was given four hours before or after the administration of gastric juice mixtures. In the cases of Hall *et al.* the mixtures were given only one hour before the morning meal and the patients were allowed meat and eggs later in the day. Thus the effects attributed to gastric juice and vitamin B_{12} may have been partly due to the interaction of gastric juice with other extrinsic factor(s) in food.

Author	Case	Haemopoietic Response				Oral Therapy		Apparent Ratio	Correction Based on Responsiveness to Injected B_{12}	Corrected Ratio	Presumed Absorption (approx.)	
		B_0	Retic. Peak	I_{10}	I_{12}	Gastric Juice Given (ml.)	B_{12} (μg.)	Total Oral Dose Given (μg.) : Parenteral Dose Expected to Give Similar Response (μg.)	Dose Injected (μg.) : Dose Expected to Give Similar Response (μg.)	Oral Dose : Parenteral Dose (approximate)	Per Dose (μg.)	%
Berk *et al.*	101	1·82	9·3	0·90	—	150×10	5×10	50 : 10	No record	—	1†/5	20†
,,	102	1·65	16·7	0·80	—	150×10	5×10	50 : 5	,, ,,	—	0·5†/5	10†
,,	103	1·90	3·8	0·64	—	150×10	5×10	50 : 5	,, ,,	—	0·5†/5	10†
,,	104	2·14	3·8	0·04	—	125×10	5×10	50 : Possibly 1·25	5×10 : Less than 5 =50	Doubtful	Doubtful	Doubtfu
Hall *et al.*	Fig. 2	1·50	31·7	—	0·86*	150×15	5×15	75 : 5	No record	—	0·3†/5	6†
,,	Fig. 4	1·63	16·5	—	1·37*	150×15	5×15	75 : 20	,, ,,	—	1·2†/5	24†
Ungley	401	1·27	13·4	1·16	—	50×10	5×10	50 : 20	5×10 : 20 =50	1 : 1	5/5	100
,,	201	1·41	18·2	—	1·22	50×15	5×15	75 : 10	40 : 5	About 1 : 1	5/5	100
,,	202	2·05	5·2	—	1·61	500	50	50 : More than 40	R.B.C. level too high	—	Over 40†/50	Over 80†
,,	303	2·55	1·8	—	−0·11	500	50	50 : Nil	50 : More than 80	Oral therapy failed	0/50	Nil
,,	304	2·25	7·8	—	0·59	500	50	50 : Less than 5	50 : Less than 5	About 1 or 2 : 1	About 25 or 50/50	50 to 100
,,	305	1·88	7·4	—	0·95	500	50	50 : 5	50 : More than 40	10 : 1	5/50	10
,,	404	1·34	15·8	—	0·82	500	80	80 : Less than 5	80 : 40	More than 8 : 1	Less than 10/80	Less than 15
,,	402	1·68	7·0	—	−0·03	150	40	40 : Possibly 1·25	40 : 40	Possibly 30 : 1 (Insufficient gastric juice)	Possibly 1·25/40	Possibly 3

* From graph. † Ratios and absorption figures marked † are uncorrected, because the actual response to parenteral therapy was not observed.

Except in one patient (Case 404) who received juice stored for 14 days, the juice was either fresh or not more than three days old. Other workers have used pooled gastric juice which may have been stored. Campbell, Hall, and Morgan (1949) state that the intrinsic factor in gastric juice is not destroyed by storage at 5° C. for three months, but did not indicate whether there is a lessening of activity.

Hall *et al.* (1949) found that Berkefeld-filtered gastric juice was active in a proportion of 150 ml. per 5 μg. of vitamin B_{12}, but comparisons with unfiltered gastric juice are not mentioned. In our Case 201 Seitz filtration of gastric juice apparently led to loss of all or most of its intrinsic factor activity.

How Efficiently is Vitamin B_{12} Absorbed When Given Orally With Gastric Juice?

It is obvious from the Table that the results are very variable. In four out of eight of my patients the effect of vitamin B_{12} given orally with gastric juice was about as effective as if the same dose of vitamin had been injected into these patients. In two others the corrected oral-dose/parenteral-dose ratio was about 10 : 1. In one case oral therapy failed completely, and in another the amount of gastric juice was too small.

Calculations similar to those used for my cases can be applied to the first three cases reported by Berk *et al.* (1948). These patients received 5 μg. of vitamin B_{12} with 150 ml. of normal gastric juice daily for 10 days. The increase in red blood cells in 10 days was approximately equivalent to that which would have been expected from single injections of 10, 5, and 5 μg. In other words, the amounts of vitamin B_{12} given orally with gastric juice were approximately 5, 10, and 10 times as great as would probably have been needed to produce a similar response with injected material. This is assuming that the patients of Berk *et al.* would have been normally responsive to injected vitamin B_{12}. Their fourth case is excluded from discussion because of the poor response not only to orally but to parenterally administered material.

In one of Hall, Morgan, and Campbell's cases the increase of red blood cells in 15 days after a total of 75 μg. with gastric juice was less than would be expected from 5 μg. by injection. In another case the response to a total of 75 μg. with gastric juice was slightly less than would have been expected from 20 μg. by injection. The apparent oral-dose/injection-dose ratios were approximately 15 and 3.75, but the actual responsiveness of these patients to injected material was not determined.

Some of the factors which may have contributed to the difference in the results obtained by the three observers have already been discussed.

How Much Juice is Needed?

This can roughly be estimated from (*a*) the total amount of gastric juice given, and (*b*) the amount of vitamin B_{12} absorbed (judging this by the haemopoietic response and correcting for "resistance," if any).

In the cases of Berk *et al.* (1948) and Hall *et al.* (1949) a correction for responsiveness to injected vitamin B_{12} was possible in only one instance. So far as one can judge from the uncorrected oral-dose/parenteral-dose ratio each 100 ml. of gastric juice seems to have been enough for the absorption of only 1 μg. or less. In all their patients and in the first two of mine the material was given daily and not as a single dose.

In Case 401 a total of 50 μg. was adequately absorbed when administered with a total of 500 ml. of gastric juice. In other words, each 100 ml. was enough for the absorption of 10 μg. Similar calculations for all my cases in the Table suggest that 100 ml. of gastric juice was enough for the absorption of the following amounts of vitamin B_{12} (μg.): 10, 10, 10, *nil*, 5 or 10, 1, less than 2, less than 1.

It is interesting to compare these figures with those of Ternberg and Eakin (1949) for the vitamin B_{12}-binding power of samples of normal gastric juice, which were: 2, 6 (pooled sample from at least three subjects), 6, and 1.5 μg. per 100 ml. of gastric juice.

It will be even more interesting, in the future, to measure microbiologically in this way the activity of samples of gastric juice which are to be clinically tested for their power to promote absorption of vitamin B_{12} in pernicious anaemia.

Summary and Conclusions

The effect of vitamin B_{12} given with normal gastric juice was observed in eight patients with pernicious anaemia. The total amounts were usually 50 μg. + 500 ml. given as a single dose or in divided doses.

One patient failed to respond to oral therapy. In one who received 40 μg. with only 150 ml. of gastric juice the response was very poor. In two the oral-dose/parenteral-dose ratio was about 10:1, suggesting that about 10% of the vitamin had been absorbed. In the remaining four the response was about as good as would have been expected if the same dose of vitamin B_{12} had been injected. Thus small doses of vitamin B_{12} given with normal gastric juice are *sometimes* efficiently absorbed.

In these eight experiments each 100 ml. of gastric juice seemed to be enough for the absorption of 0, less than 1, 1, less than 2, 5 or 10, 10, 10, and 10 μg. of vitamin B_{12}. Thus the amount of gastric juice necessary to promote the absorption of a given amount of B_{12} varied considerably. These variations are perhaps only partly due to differences in the amount of intrinsic factor in the samples of gastric juice; differences in the recipients may have been equally important.

III. FAILURE OF FRESH MILK OR CONCENTRATED WHEY TO FUNCTION AS CASTLE'S INTRINSIC FACTOR OR TO POTENTIATE THE ACTION OF ORALLY ADMINISTERED VITAMIN B_{12}

BY

C. C. UNGLEY, M.D., F.R.C.P.

Physician, Royal Victoria Infirmary, Newcastle-upon-Tyne

With the assistance of

G. A. CHILDS

Chemist, Research Division, Glaxo Laboratories, Greenford, Middlesex

In another paper we have confirmed the findings of Ternberg and Eakin (1949) that normal gastric juice combines with vitamin B_{12} and renders it unavailable to certain bacteria (Ungley and Cuthbertson, 1950: Paper V of this series, to be published).

The possibility that milk might have similar properties has been investigated. For this purpose microbiological tests proved useless, milk being an unsatisfactory material for the microbiological assay of vitamin B_{12}. Nevertheless, exploratory clinical tests have been made to determine whether milk would be effective as a source of Castle's intrinsic factor.

Methods

A general account of methods is given in Paper I.

For the first two tests fresh cow's milk was cooled quickly immediately after milking and kept in a vacuum flask for not more than four hours before administration.

For the first whey concentrate 7.5 litres of skimmed milk was treated at 37° C. with 455 ml. of diluted acetic acid to *p*H 4.5. The casein was filtered off to yield 6,800 ml. of crude whey. The whey was concentrated at *p*H 6.5 to 790 ml. and dialysed against distilled water overnight at 4° C. to eliminate salts and some of the lactose. During dialysis a precipitate composed mainly of lactose and lactoglobulin came down. This precipitate was combined with the concentrated supernatant fluid to make a total volume of approximately 650 ml., representing 7 litres of milk.

The second whey concentrate was prepared from 22 litres of milk. The casein was removed and the whey evaporated to small bulk at low temperature. This concentrated whey was then dialysed to remove most of the lactose.

Results

Two patients received fresh milk and three cases were given whey concentrates, in each case with added vitamin B_{12}.

Case 301

A woman aged 58 had pernicious anaemia with minor neurological involvement. The dietary history was normal. In a control period of 14 days, during which reticulocytes did not exceed 3.4%, the red blood cells fell from 1,610,000 to 1,070,000 per c.mm. After transfusion the count rose to 2,300,000 per c.mm. (Fig. 1). After a further control period of 13 days during which reticulocytes did not exceed 1.6%, the red blood cells numbered 1,480,000 per c.mm., haemoglobin 5.6 g. per 100 ml., reticulocytes 1%, M.C.V. 131.7 μ^3, M.C.H. 37.9 $\mu\mu$g., M.C.H.C. 28.2%, white blood cells 2,800 per c.mm. The marrow was megaloblastic.

In the first period she was given daily 500 ml. of preserved fresh milk to which 10 μg. of vitamin B_{12} was added before administration. There was a slight reticulocytosis, reaching 3% on the eighth and ninth days with little change in the anaemia.

In the second period she received daily 500 ml. of preserved fresh milk to which 100 μg. of folic acid was added before administration. There was no second reticulocyte response, but the anaemia improved.

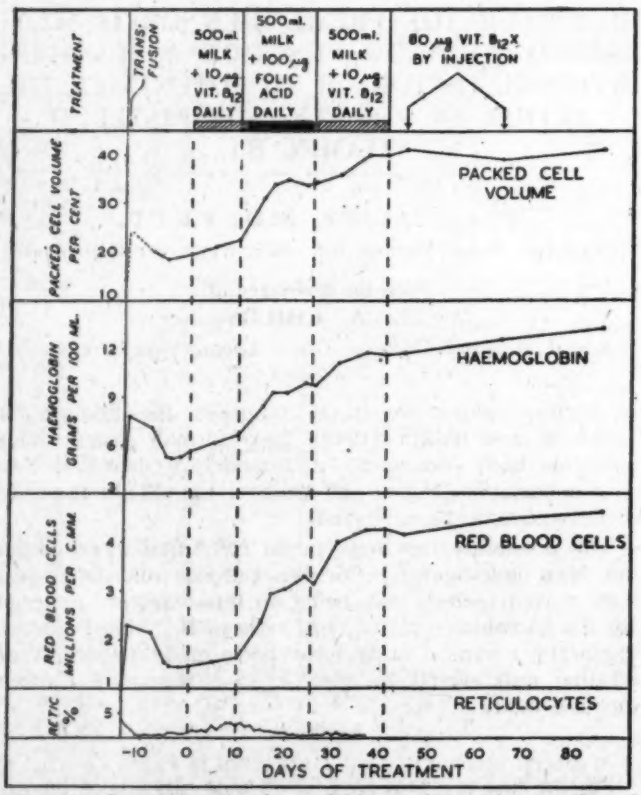

TREATMENT
TRANS-FUSION
500 ml. MILK + 10 μg VIT. B12 DAILY
500 ml. MILK + 100 μg FOLIC ACID DAILY
500 ml. MILK + 10 μg VIT. B12 DAILY
80 μg VIT. B12 X BY INJECTION
PACKED CELL VOLUME PER CENT
PACKED CELL VOLUME
HAEMOGLOBIN GRAMS PER 100 ML.
HAEMOGLOBIN
RED BLOOD CELLS MILLIONS PER C.MM.
RED BLOOD CELLS
RETIC %
RETICULOCYTES
-10 0 10 20 30 40 50 60 70 80
DAYS OF TREATMENT

Fig. 1.—Case 301. Showing a fairly continuous increase in red blood cells during treatment, with only a slight reticulocytosis. This may have been a spontaneous remission.

Days:	First Period 0	5	Second Period 10	15	20	35
R.B.C. (mills./c.mm.)	1·48	1·54	1·62	2·39	3·03	3·23
Hb (g./100 ml.)	5·6	6·2	6·7	8·4	9·3	9·9
P.C.V. (%)	19·5	21·0	22·5	31·0	35·0	34·5

In the third period treatment reverted to the daily administration of 500 ml. of preserved fresh milk plus 10 μg. of vitamin B_{12}. The anaemia continued to improve.

Days:	Third Period 0	5	10	15
R.B.C. (mills./c.mm.)	3·16	4·00	4·24	4·26
Hb (g./100 ml.)	9·8	11·1	11·8	11·8
P.C.V. (%)	34·5	36·0	40·0	40·0

Comment.—The slight reticulocytosis in the first period might equally well have occurred from the daily oral administration of 10 μg. of vitamin B_{12} alone, without the milk. In the absence of any further reticulocyte response the improvement in the second and third periods cannot safely be attributed to treatment. Spontaneous remission is a distinct probability.

Case 302

A retired labourer aged 65 had pernicious anaemia without neurological involvement. The dietary history was normal.

After a control period of five days, during which the reticulocytes did not exceed 1%, the red blood cells numbered 2,010,000 per c.mm., haemoglobin 7.8 g. per 100 ml., reticulocytes 0.6%, M.C.V. 111.9 μ^3, M.C.H. 39.1 $\mu\mu$g., M.C.H.C. 34.7%, white blood cells 5,100 per c.mm. The marrow was megaloblastic.

In the first period he was given daily for 15 days 500 ml. of preserved fresh milk to which 10 μg. of vitamin B_{12} was added before administration. There was a slight reticulocytosis reaching 4.6% on the seventh day, but no increase of red blood cells (Fig. 2).

Days:	First Period 0	5	10	15
R.B.C. (mills./c.mm.)	2·01	1·86	1·78	1·93
Hb (g./100 ml.)	7·8	7·0	6·5	7·0
P.C.V. (%)	22·5	22·0	22·5	22·5

In the second period 1 μg. of vitamin B_{12} daily was given parenterally for 15 days. There was a second reticulocytosis of 4.6% on the eighth day, followed by subjective improvement and some increase in red blood cells.

Days:	Second Period 0	5	10	15	Third Period 20	25	30
R.B.C. (mills./c.mm.)	1·93	2·18	2·31	2·33	2·87	3·28	3·36
Hb (g./100 ml.)	7·0	8·0	8·9	9·3	10·7	11·3	11·7
P.C.V. (%)	22·5	24·0	28·0	29·0	33·0	34·0	36·0

In the third period 0.8 μg. of vitamin B_{12} plus 100 μg. of folic acid daily was given for 15 days. There was no reticulocytosis. The red blood cells continued to increase.

Comment.—In this case fresh milk was clearly not a satisfactory source of Castle's intrinsic factor. The reticulocyte response of 4.6% was no greater than might have been expected from the vitamin B_{12} alone, and there was no increase of red blood cells in 15 days.

The remaining cases were given whey concentrate instead of fresh milk.

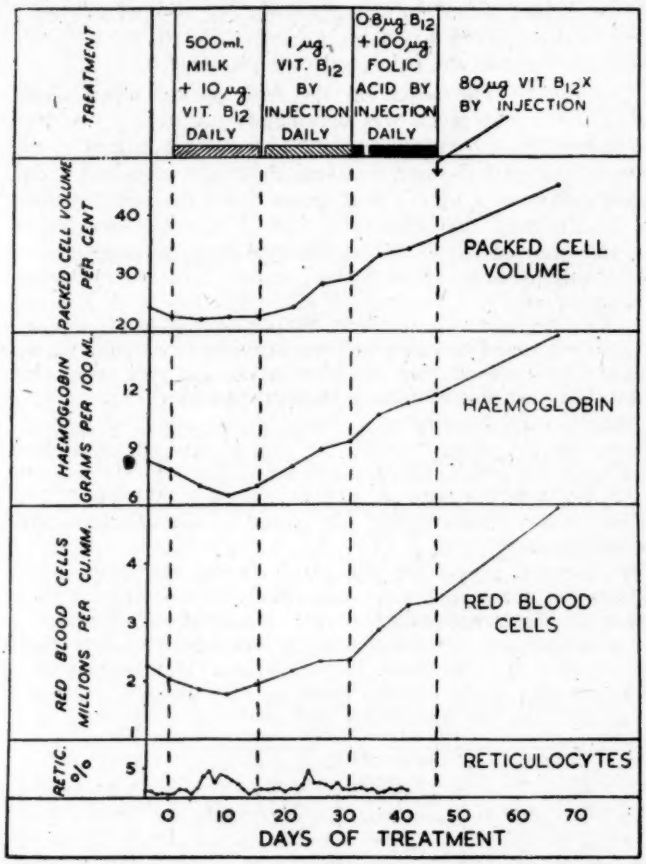

TREATMENT
500 ml. MILK + 10 μg. VIT. B12 DAILY
1 μg. VIT. B12 BY INJECTION DAILY
0·8 μg B12 + 100 μg FOLIC ACID BY INJECTION DAILY
80 μg VIT B12 X BY INJECTION
PACKED CELL VOLUME PER CENT
PACKED CELL VOLUME
HAEMOGLOBIN GRAMS PER 100 ML.
HAEMOGLOBIN
RED BLOOD CELLS MILLIONS PER CU.MM.
RED BLOOD CELLS
RETIC. %
RETICULOCYTES
DAYS OF TREATMENT

FIG. 2.—Case 302. The administration of milk and vitamin B_{12} produced only a small reticulocytosis without rise of red blood cells. Following the daily injection of 1 μg. vitamin B_{12} there was a secondary reticulocytosis, but the increase of red blood cells was below expectation. There was no further reticulocytosis when part of the vitamin B_{12} was replaced by folic acid.

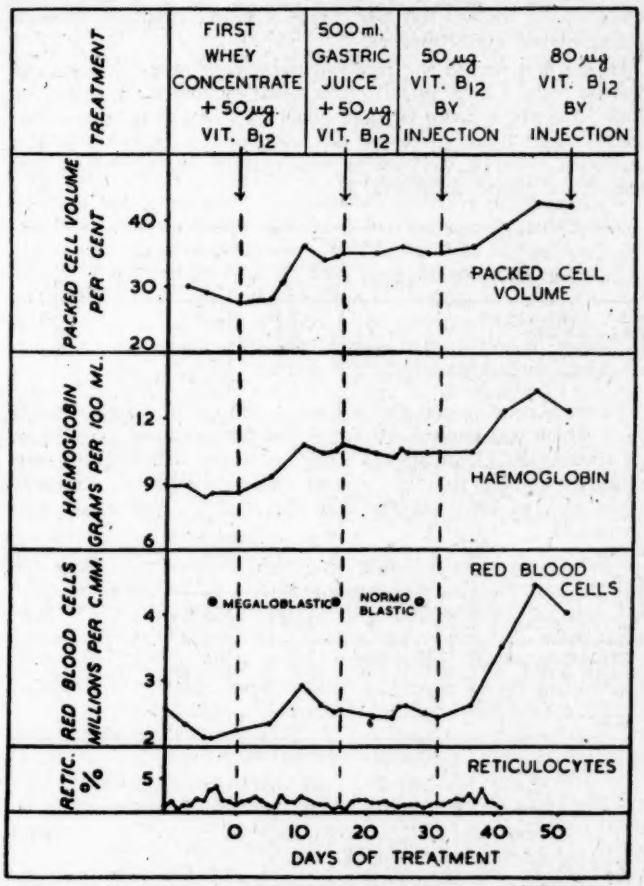


FIG. 3.—Case 303. In the control period there was a small spontaneous reticulocytosis without a rise of red blood cells. Following the administration of the whey concentrate with vitamin B_{12} there was a transient increase of red blood cells but no reticulocytosis, and the marrow remained megaloblastic. Vitamin B_{12} with gastric juice had no effect on reticulocytes or red blood cells, but the marrow became normoblastic. The response to an injection of 50 μg. of vitamin B_{12} was better than expectation.

Case 303

A housewife aged 73 had pernicious anaemia without neurological involvement. She ate little meat or cheese, and no eggs or tomatoes.

After a control period of 12 days, during which the reticulocytes did not exceed 3.8%, the red blood cells numbered 2,270,000 per c.mm., haemoglobin 8.6 g. per 100 ml., reticulocytes 1%, M.C.V., 121.1 μ^3, M.C.H. 37.9 μμg., M.C.H.C. 31.2%, white blood cells 5,100 per c.mm. The marrow was megaloblastic.

In the first period she received a whey concentrate derived from 7 litres of milk to which was added 50 μg. of vitamin B_{12}. The mixture stood at room temperature for seven hours and was then given by stomach tube approximately eight hours after the last meal and eight hours before breakfast. There was a slight variable reticulocytosis of 2.6% on the seventh day and some improvement in the anaemia (Fig. 3). The marrow remained megaloblastic.

	First Period				Second Period			
Days:	0	5	10	15	16	21	26	31
R.B.C. (mills./c.mm.)	2·27	2·36	2·92	2·51	2·55	2·45	2·61	2·44
Hb (g./100 ml.)	8·6	9·3	10·8	10·5	10·8	10·4	10·4	10·4
P.C.V. (%)	27·5	28·0	36·0	34·5	35·0	35·0	36·0	35·0

In the second period she received 500 ml. of normal gastric juice with 50 μg. of vitamin B_{12}; the mixture was left at room temperature for seven and a half hours and given by stomach tube in the same manner as before. There was no reticulocytosis and no rise of red blood cells in 15 days; after 12 days the marrow picture was predominantly normoblastic and macronormoblastic.

In the third period 50 μg. of vitamin B_{12} was given parenterally. A slight reticulocytosis of 3.4% on the seventh day was followed by a good increase in red blood cells.

	Third Period			
Days:	0	5	10	15
R.B.C. (mills./c.mm.)	2·44	2·61	3·50	4·41
Hb (g./100 ml.)	10·4	10·4	12·3	13·2
P.C.V. (%)	35·0	36·0	39·0	42·5

Comment.—The result in the first period, when whey concentrate was given as a possible source of Castle's intrinsic factor, was probably negative, the response being no greater than might be expected from the vitamin B_{12} alone, but for some reason the patient did not respond to B_{12} and gastric juice. She was not "resistant" to vitamin B_{12}, for the increase in red blood cells after an injection of 50 μg. was greater than would be expected from an injection of 80 μg.

Case 304

A housewife aged 67 had pernicious anaemia with minor neurological involvement. She ate very little meat or vegetables.

After a control period of 11 days, during which the reticulocytes did not exceed 1.2%, the red blood cells numbered 2,460,000 per c.mm., haemoglobin 8.9 g. per 100 ml., reticulocytes 1%, M.C.V. 118 μ^3, M.C.H. 36.1 μμg., M.C.H.C. 30.6%,

white blood cells 3,700 per c.mm. Sternal marrow showed megaloblastic erythropoiesis.

In the first period she received the second whey concentrate derived from 3 litres of milk which was incubated for one hour with 50 μg. of vitamin B_{12} and given by stomach tube approximately eight hours after the last meal and eight hours before breakfast. In 10 days there was neither reticulocytosis nor rise of red blood cells (Fig. 4).

	First Period		
Days:	0	5	10
R.B.C. (mil'ns/c.mm.)	2·46	2·34	2·21
Hb (g./100 ml.)	8·9	9·3	8·9
P.C.V. (%)	29·0	28·0	27·0

In the second period she was given 500 ml. of normal gastric juice which was neutralized, incubated for one hour with 50 μg. of vitamin B_{12}, kept at 5° C. for seven and a half hours, and given by stomach tube in the same manner as before. Reticulocytes rose to 7.8% on the sixth day and the red blood cells increased.

	Second Period				Third Period		
Days:	0	5	10	15	20	25	30
R.B.C. (mills./c.mm.)	2·25	2·34	2·73	2·84	3·05	3·79	3·47
Hb (g./100 ml.)	8·7	8·9	10·4	9·9	10·8	12·1	11·1
P.C.V. (%)	27·0	27·0	33·0	29·0	32·0	36·0	36·0

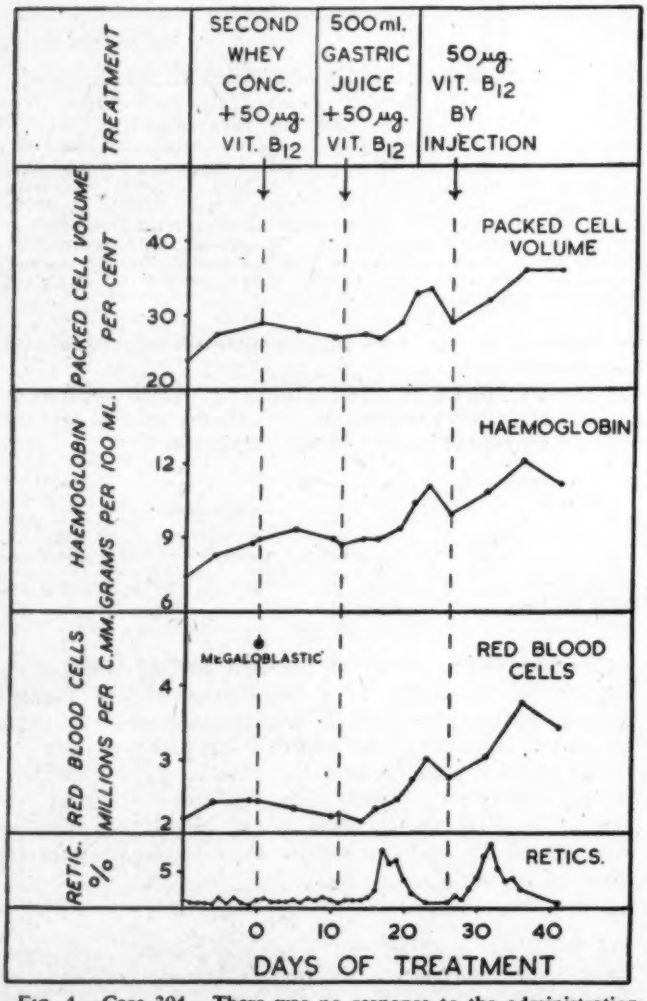


FIG. 4.—Case 304. There was no response to the administration of a whey concentrate and vitamin B_{12}. The response to 50 μg. of vitamin B_{12} with gastric juice was less than that which would be expected from an injection of 5 μg. The response to 50 μg. of vitamin B_{12} by injection was below expectation.

In the third period 50 μg. of vitamin B_{12} was administered parenterally. There was a second reticulocytosis of 8.6% on the sixth day and the red blood cells increased.

Comment.—The result in the first period when whey concentrate was given was completely negative. The rise of red blood cells after giving 50 μg. of vitamin B_{12} and 500 ml. of gastric juice was less than that expected from an injection of 5 μg. The response from the injected dose of 50 μg. was also slightly less than that expected from an injection of 5 μg. Thus the oral-dose/parenteral-dose ratio was probably 1 or 2 : 1.

Case 305

A woman aged 60 had pernicious anaemia with minor neurological involvement. She ate little meat, eggs, fish, cheese, or fruit, but plenty of milk, cereals, and vegetables.

After a control period of nine days, during which the reticulocytes did not exceed 1.6%, the red blood cells numbered 1,810,000 per c.mm., haemoglobin 6.5 g. per 100 ml., reticulocytes 0.6%, M.C.V. 116 μ^3, M.C.H. 32.8 $\mu\mu$g., M.C.H.C. 31%, white blood cells 4,000 per c.mm. The marrow was megaloblastic.

In the first period she was given on two successive nights 575 ml. of the second whey concentrate derived from 3 litres of milk which was incubated for one hour with 25 μg. of vitamin B_{12} and given by stomach tube approximately eight hours after the last meal and eight hours before breakfast. There was a slight reticulocytosis of 4.6% on the sixth day (Fig. 5). The red blood cells had increased at the tenth day.

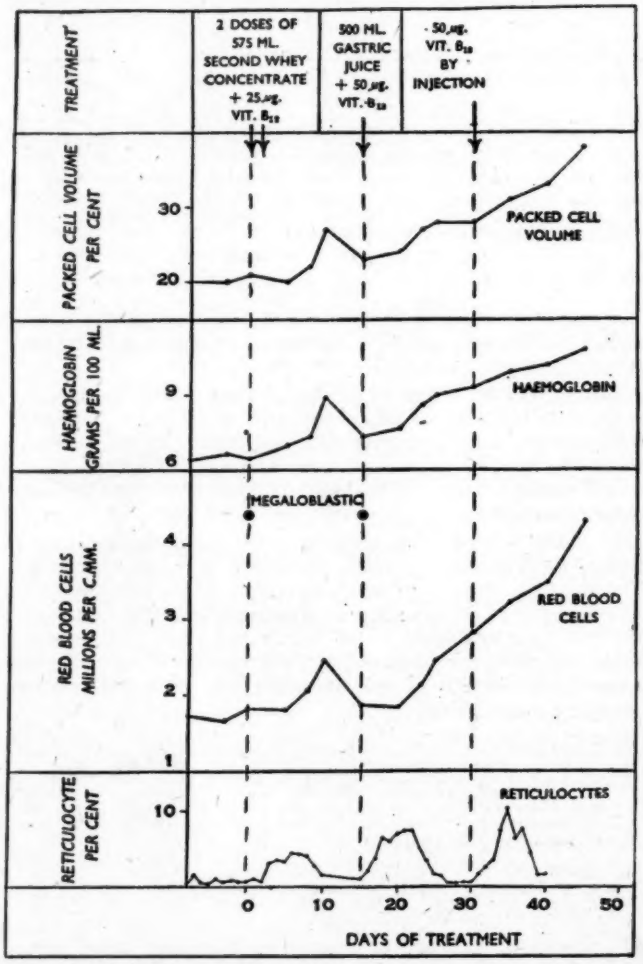

TREATMENT
2 DOSES OF 575 ML. SECOND WHEY CONCENTRATE + 25 µg. VIT. B12
500 ML. GASTRIC JUICE + 50 µg. VIT. B12
50 µg. VIT. B12 BY INJECTION
PACKED CELL VOLUME PER CENT
PACKED CELL VOLUME
HAEMOGLOBIN GRAMS PER 100 ML.
HAEMOGLOBIN
RED BLOOD CELLS MILLIONS PER C.MM.
MEGALOBLASTIC
RED BLOOD CELLS
RETICULOCYTE PER CENT
RETICULOCYTES
DAYS OF TREATMENT

FIG. 5.—Case 305. The response to whey concentrate with vitamin B_{12} was poor and no greater than might have been obtained by giving the vitamin B_{12} by mouth alone. The response to 50 μg. of vitamin B_{12} given with gastric juice was equivalent to that which would have been expected from an injection of 5 μg. The response to an injection of 50 μg. of vitamin B_{12} was up to expectation.

but by the fifteenth were back to their former level. The marrow was still megaloblastic.

	First Period			
Days:	0	5	10	15
R.B.C. (mills./c.mm.)	1·81	1·80	2·46	1·88
Hb (g./100 ml.)	6·5	7·0	8·9	7·4
P.C.V. (%)	21·0	20·0	27·0	23·0

In the second period she received a single dose of 500 ml. of normal gastric juice which was neutralized, incubated for one hour with 50 μg. of vitamin B_{12}, kept at 5° C. for seven hours, and given by stomach tube eight hours after the last meal and eight hours before breakfast. Reticulocytes rose to a second peak of 7.4% on the sixth and seventh days, and this time the improvement in the anaemia was sustained.

	Second Period			Third Period			
Days:	0	5	10	15	20	25	30
R.B.C. (mills./c.mm.)	1·88	1·86	2·46	2·83	3·21	3·50	4·32
Hb (g./100 ml.)	7·4	7·7	9·0	9·3	9·9	10·2	10·8
P.C.V. (%)	23·0	24·0	28·0	28·0	31·0	33·0	38·0

In the third period 50 μg. of vitamin B_{12} was given parenterally. Reticulocytes rose to 10.2% on the fifth day. Improvement in the anaemia was accelerated.

Comment.—The result with the whey concentrate plus vitamin B_{12} was regarded as negative as there was only a slight reticulocytosis of 4.6% with no rise of red blood cells in 15 days—that is, a very slight response which might well have occurred from the oral administration of similar doses of vitamin B_{12} without the whey concentrate. In the second period the rise in red blood cells after giving 50 μg. of vitamin B_{12} plus 500 ml. of gastric juice was equivalent to that expected from an injection of 5 μg. In the third period the response to the injected dose of 50 μg. was greater than expected. The patient therefore was not "resistant," and the oral-dose/parenteral-dose ratio was probably about 10 : 1.

Conclusions

Neither fresh milk nor a whey concentrate in the doses given was an adequate substitute for normal human gastric juice as a source of Castle's intrinsic factor.

IV. ADMINISTRATION INTO BUCCAL CAVITY, INTO WASHED SEGMENT OF INTESTINE, OR AFTER PARTIAL STERILIZATION OF BOWEL

BY

C. C. UNGLEY, M.D., F.R.C.P.

Physician, Royal Victoria Infirmary, Newcastle-upon-Tyne

The object of these experiments was to determine whether vitamin B_{12} even without intrinsic factor would be efficiently absorbed if destruction by intestinal contents could be avoided or reduced. This was attempted in three ways: (1) by the application of vitamin B_{12} to the buccal mucosa; (2) by instillation into a washed segment of the intestine; and (3) by the oral administration of vitamin B_{12} after preliminary partial sterilization of the gut.

Methods

A general account of methods is given in Paper I.

For *buccal administration*, vitamin B_{12} was applied daily to the floor of the mouth in the sulcus between the alveolar margin and the cheek. Over a period of 30 minutes a solution containing 5.5 μg. was added gradually by syringe to a pledget of cotton-wool lying on the mucous membrane which formed the base of an artificial cavity created by a dental appliance, designed to prevent leakage from the sulcus. For the next 30 minutes water alone was added. Afterwards the cotton-wool pledgets were stored for microbiological assay by Dr. W. F. J. Cuthbertson, 10 pledgets yielding 8 μg. of vitamin B_{12}.

There were four experiments in which B_{12} with or without gastric juice was *instilled into a washed segment of intestine.* In Case 402 a Miller–Abbott tube with two balloons was passed until *x*-ray examination confirmed that the end was in the small intestine. The balloons were inflated, and the intervening section of intestine was washed out with normal saline until the washings were clear. Then a solution of 40 μg. of vitamin B_{12} in 10 ml. of water was instilled, followed by water to wash through the tube. After one hour the remaining material was aspirated and the segment washed out again. A sample of the aspirate contained 0.5 μg. of vitamin B_{12} per ml.

In the second period the Miller–Abbott tube was again passed into the small intestine and the balloons were inflated as before. After washing out, the segment between the balloons was filled with 150 ml. of Seitz-filtered normal gastric juice mixed with 40 μg. of vitamin B_{12}.

In Case 403 in the first period a Miller–Abbott tube with two balloons attached 15 cm. apart was passed as in Case 402 until the end was well down the small intestine. The balloons were inflated and the intervening section of intestine was washed out with 200 ml. of normal saline until the washings were almost clear. Then 80 μg. of vitamin B_{12} in 10 ml. of normal saline was instilled, followed by 30 ml. of saline to wash through the tube (approximately 10 ml. would remain in the tube). After two hours the material remaining in the segment of intestine was aspirated, and the segment was washed again. The aspirate contained 0.45 μg. of vitamin B_{12} per ml.

In the second period a Miller–Abbott tube was passed as before but with the balloons 30 cm. apart. Intestinal juice collected on the way down contained 0.01 μg. of vitamin B_{12} per ml. The balloons were inflated and the segment was washed out with 500 ml. of distilled water, of which 300 ml. was recovered and found to contain 0.018 μg. of vitamin B_{12} per ml. Then 40 μg. of vitamin B_{12} in 250 ml. of normal gastric juice adjusted to *p*H 7 was instilled very slowly into the segment and left in place for one hour. Aspiration after one hour yielded 14 ml. of clear yellow fluid containing 0.05 μg. of vitamin B_{12} per ml. Washings yielded 35 ml. of clear pale yellow fluid containing no vitamin B_{12}. A further 40 μg. of vitamin B_{12} with 250 ml. of normal gastric juice was instilled. This caused colic, and the patient vomited 150 ml. of dark-brown fluid containing approximately 0.001 μg. or less of vitamin B_{12} per ml. Aspiration after one hour yielded 20 ml. of dark-brown fluid containing 0.025 μg. of vitamin B_{12} per ml. The segment was again washed out with 500 ml. of water, 118 ml. of which, containing 0.02 μg. of vitamin B_{12} per ml., was recovered.

An attempt to *sterilize the small intestine* is described in Case 404.

Application of Vitamin B_{12} to Buccal Mucosa

Case 401

A farm labourer aged 50 had pernicious anaemia with sore tongue but no neurological involvement. The dietary history was normal.

After a satisfactory control period of 11 days the red blood cells numbered 1,620,000 per c.mm., haemoglobin 5.9 g. per 100 ml., M.C.H. 36 $\mu\mu$g., M.C.V., 111 μ^3, M.C.H.C. 32.9%, reticulocytes 0.4%, and white blood cells 1,800 per c.mm. The marrow was megaloblastic.

After the daily instillation of approximately 5 μg. of vitamin B_{12} into the buccal cavity there was a negligible reticulocytosis of 2.8% on the tenth day and the red blood cells fell to 1,270,000 per c.mm. (Fig. 1).

In the second period the patient received 5 μg. of vitamin B_{12} daily mixed with 50 ml. of unfiltered gastric juice, neutralized

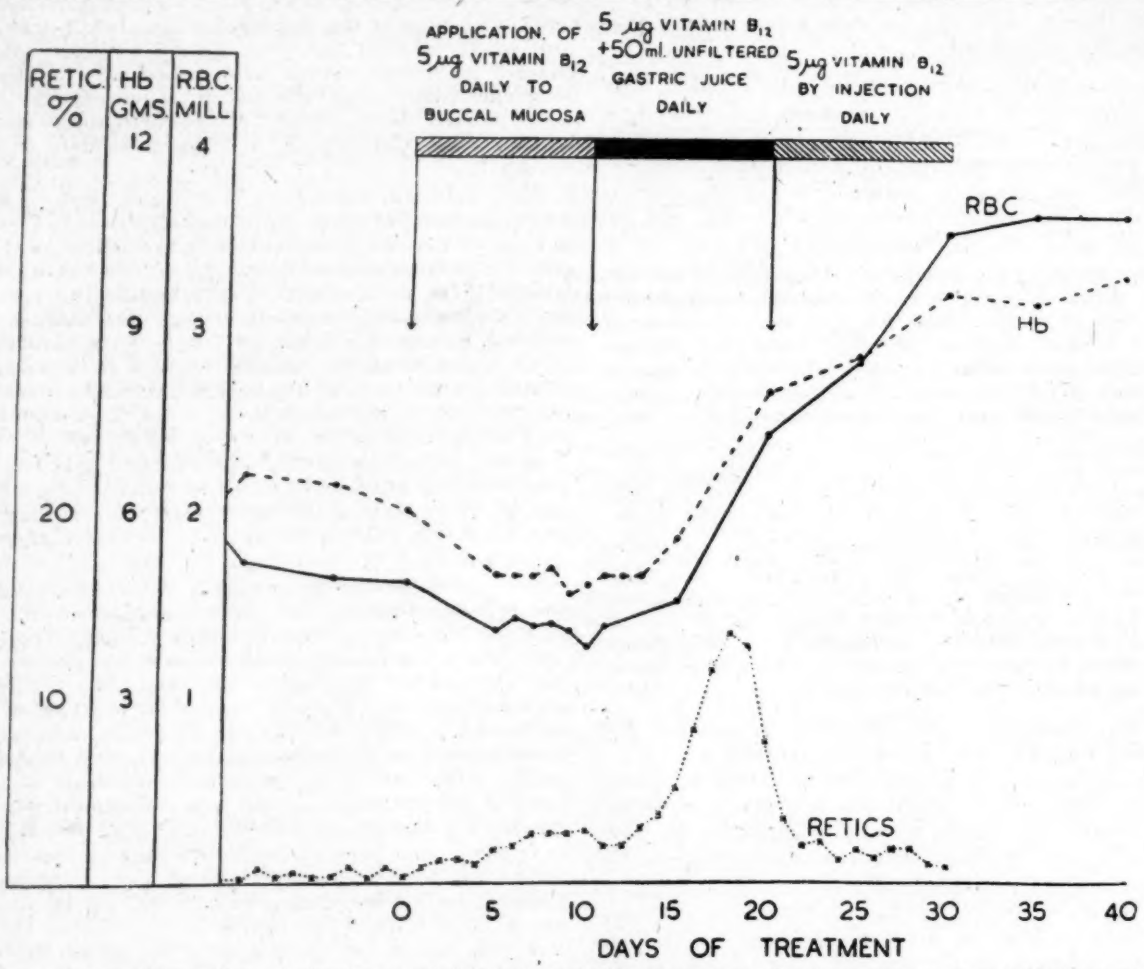


FIG. 1.—Case 401. Failure of vitamin B_{12} administered via the buccal mucosa. Good response to same dose of vitamin B_{12} given with gastric juice.

just before administration. The reticulocytes began to rise on the fourth day, reaching a peak of 13.4% on the eighth day. There was subjective improvement and the red blood cells increased.

	←Second Period→		←Third Period→		←Nil→		
Days:	0	5	10	15	20	25	30
R.B.C. (mills./c.mm.)	1·27	1·52	2·43	2·83	3·54	3·64	3·63
Hb (g./100 ml.) ..	4·7	5·5	7·8	8·4	9·5	9·3	9·8
P.C.V. (%)	14·0	—	25·0	29·1	31·0	32·5	35·0

In the third period he was given injections of 5 μg. of vitamin B_{12} daily for 10 days. There was no secondary reticulocytosis. The red blood cells continued to increase. Subsequent treatment with vitamin B_{12} brought the counts to normal.

Comment.—The absence of haemopoietic response in the first period suggested that little, if any, vitamin B_{12} was absorbed from the mouth. Disappearance of liquid from the chamber was not regarded as proof of absorption of vitamin B_{12}. The increase of red blood cells in 10 days after a total of 50 μg. of vitamin B_{12} given orally with gastric juice was equivalent to the response expected from a single injection of 20 μg. The adequacy of the response is further suggested by the absence of any secondary reticulocytosis in the third period when the same daily dose of vitamin B_{12} was given by injection. Incidentally the increase in red blood cells after a total of 50 μg. (plus any effect left over from the previous therapy) was equivalent only to the increase expected from 20 μg. Thus the true oral-dose/injection-dose ratio may have been close to unity; 50 μg. given orally with gastric juice and 50 μg. given by injection both produced a response equivalent to that normally expected from a single injection of 20 μg.

Instillation of Vitamin B_{12} into an Isolated Washed Segment of Intestine

This was performed twice in each of two patients.

Case 402

A man aged 54 had pernicious anaemia with minor neurological involvement. He disliked meat except bacon, but ate plenty of eggs, milk, cheese, fruit, and vegetables.

During the control period of nine days the reticulocytes were less than 1% and red blood cells fell from 2,650,000 to 2,090,000 per c.mm., with haemoglobin 7.4 g. per 100 ml., M.C.H. 35.5 μμg., M.C.V. 109 μ^3, M.C.H.C. 32.6%, and white blood cells 1,800 per c.mm.

After instillation of 40 μg. of vitamin B_{12} into a washed segment of intestine there was neither reticulocytosis nor increase of red cells (Fig. 2).

In the second period 40 μg. of vitamin B_{12} was instilled with 150 ml. of normal gastric juice. Unfortunately the gastric juice had been passed through a Seitz filter, which, as we learned subsequently, may have removed most of the intrinsic factor activity (Case 201). There was no reticulocytosis or increase of red blood cells.

In the third period the patient was given by mouth 150 ml. of unfiltered normal gastric juice neutralized just before administration and mixed with 40 μg. of vitamin B_{12}. The reticulocytes began to increase on the fourth day, reaching 7% on the sixth day. There was no increase of red blood cells, and clinical improvement was transient.

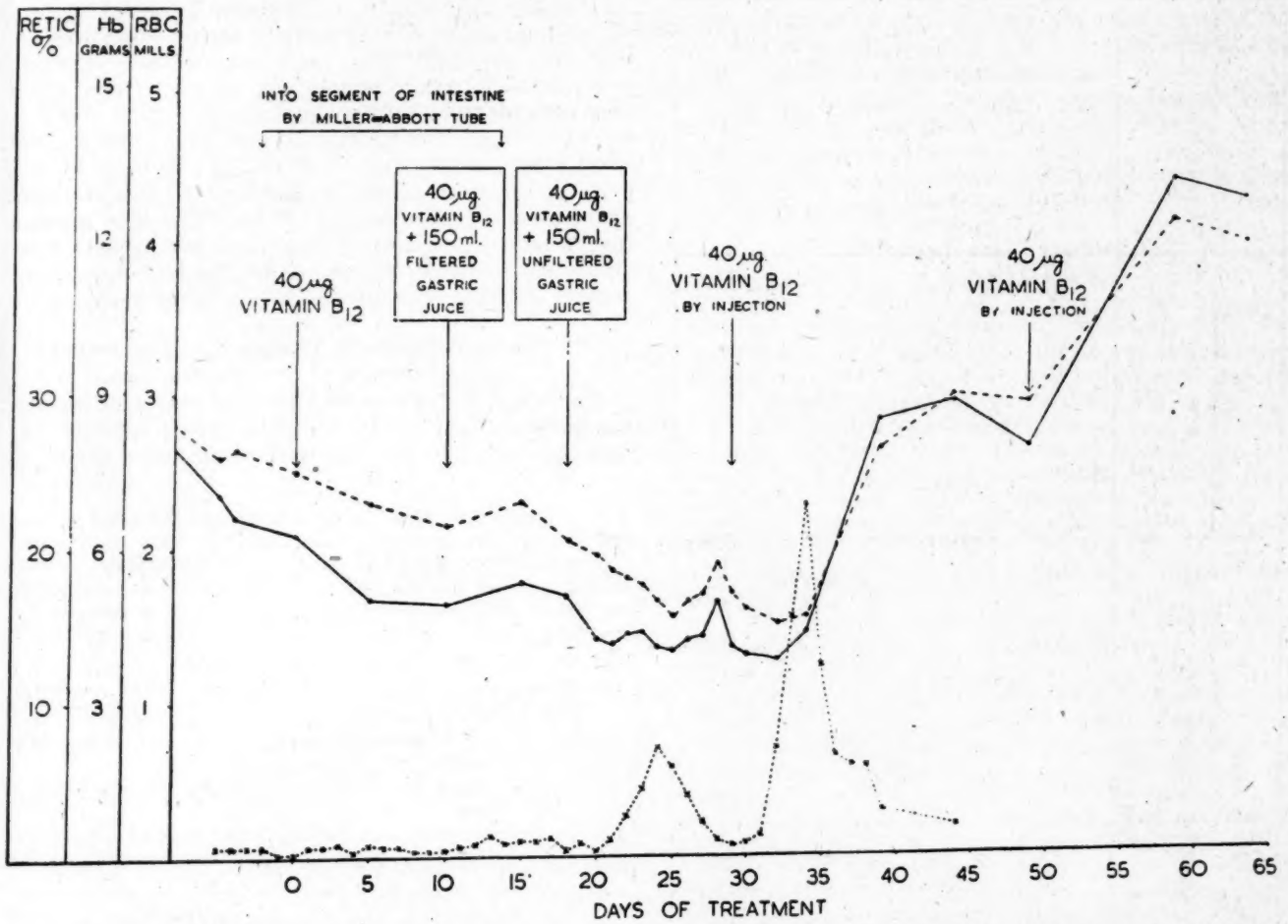

RETIC %
Hb GRAMS
RBC MILLS
INTO SEGMENT OF INTESTINE BY MILLER-ABBOTT TUBE
40 µg VITAMIN B12 + 150 ml. FILTERED GASTRIC JUICE
40 µg VITAMIN B12 + 150 ml. UNFILTERED GASTRIC JUICE
40 µg VITAMIN B12
40 µg VITAMIN B12 BY INJECTION
40 µg VITAMIN B12 BY INJECTION
DAYS OF TREATMENT

FIG. 2.—Case 402. Failure of vitamin B_{12} administered into an isolated washed segment of small intestine—either alone or with Seitz-filtered (and thus probably inactivated) gastric juice. Poor response to same dose of vitamin B_{12} given orally with 150 ml. of unfiltered gastric juice. (150 ml. is probably not enough for the absorption of 40 µg.) Normal response to injection of 40 µg.

	←Third Period→			←Fourth Period→		
Days:	0	5	11	16	21	26
R.B.C. (mills./c.mm.)	1·68	1·45	1·35	1·44	2·83	2·96
Hb (g./100 ml.) ..	6·1	5·2	5·0	4·6	7·8	8·9
P.C.V. (%)	19·0	16·5	—	18·0	30·0	31·0

In the fourth period a single injection of 40 µg. of vitamin B_{12} led to a reticulocytosis of 22.8% on the fifth day and the red blood cells increased rapidly. Further injections of vitamin B_{12} brought the counts to normal.

Comment.—Vitamin B_{12} in a dose of 40 µg. administered into a washed segment of intestine twice failed to produce a haemopoietic effect. This suggests that little or no vitamin B_{12} was absorbed. The high concentration of vitamin B_{12} in the aspirate even after one hour (see Methods) is perhaps further evidence that absorption was absent or incomplete, but one cannot be certain how efficiently the tube had been washed clear of vitamin B_{12} before the final aspiration. The poor response in the third period suggests that 150 ml. of the gastric juice used was enough for the absorption of only a small fraction of the dose of 40 µg. of vitamin B_{12}. A similar reticulocytosis without rise of red blood cells has been produced by doses as low as 1.25 or 2.5 µg. by injection. In the fourth period the increase of red blood cells in 15 days after 40 µg. by injection (plus any effect left over from previous therapy) was close to the expected increase. This suggests that there was no "resistance" to vitamin B_{12}.

Case 403

A crane-driver aged 56 had pernicious anaemia without neurological involvement. The dietary history was normal.

On admission red blood cells numbered 1,670,000 per c.mm., haemoglobin 5.9 g. per 100 ml., reticulocytes 0.4 %, P.C.V. 18%, M.C.V. 108 μ^3, M.C.H. 35.5 µµg., M.C.H.C. 33%, white blood cells 5,300 per c.mm. During a control period of 11 days the reticulocytes did not exceed 1.6% and the red cells did not increase. The marrow was megaloblastic.

After the instillation of 80 µg. of vitamin B_{12} into a washed segment of intestine reticulocytes rose slightly to 4.2% on the fifth day, but there was no increase of red cells (Fig. 3).

	←First Period→			←Second Period→		
Days:	0	5	10	14	19	25
R.B.C. (mills./c.mm.)	1·58	1·56	1·53	1·45	1·33	1·38
Hb (g./100 ml.) ..	6·2	6·4	5·9	5·6	5·3	5·9
P.C.V. (%)	19·0	19·0	18·0	18·0	17·0	17·0

In the second period the distance between the balloons was doubled and 80 µg. of vitamin B_{12} with 500 ml. of normal gastric juice was instilled in two lots for an hour each. Reticulocytes rose to a peak of 5.4% on the sixth day and after 11 days the red cell count was essentially unchanged. A further marrow puncture showed that, although there was some maturation compared with the control period, erythropoiesis was still predominantly megaloblastic.

In the third period the patient was given an intramuscular injection of 80 µg. of vitamin B_{12}. The reticulocytes rose on the third day and reached a peak of 27.8% on the sixth day. The red blood cells increased rapidly.

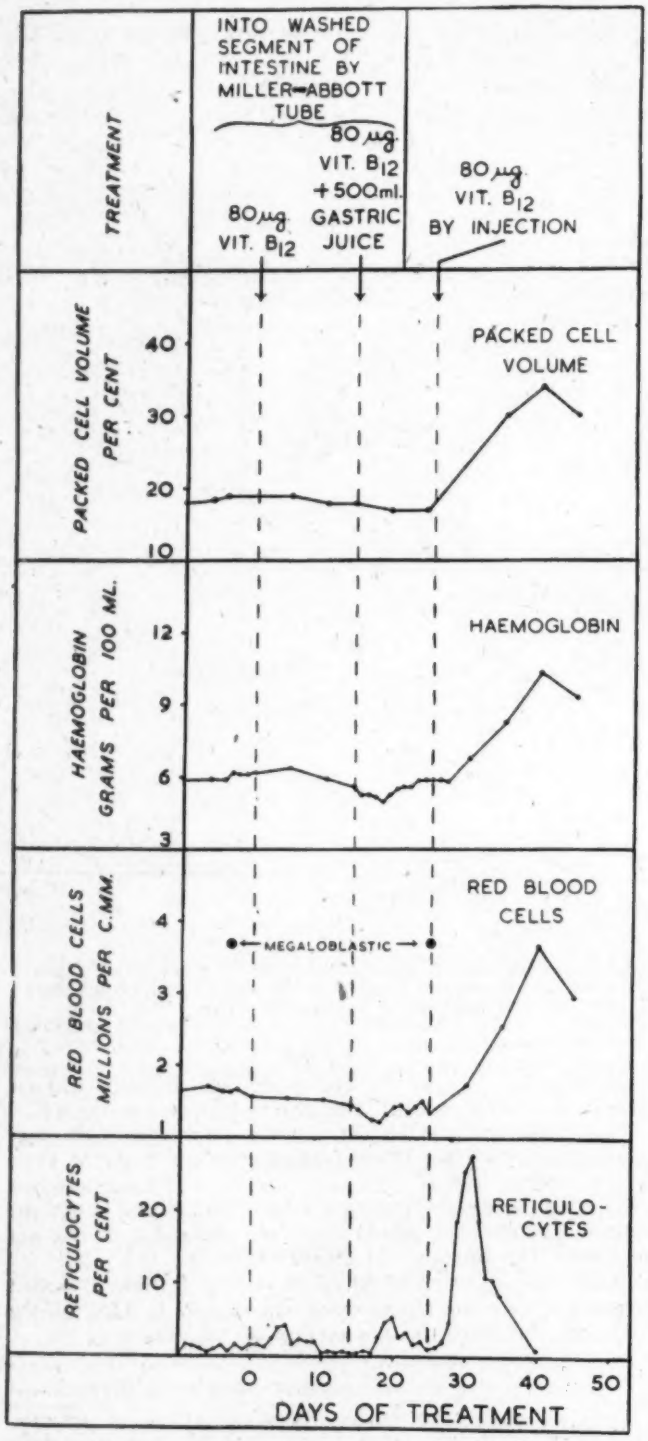


FIG. 3.—Case 403. Showing that the instillation of 80 µg. of vitamin B_{12} with or without gastric juice into a washed segment of intestine failed to produce anything more than a slight reticulocytosis. There was afterwards a good response to 80 µg. of vitamin B_{12} by injection.

	Third Period				
Days:	0	5	10	15	20
R.B.C. (mills./c.mm.)	1·38	1·76	2·58	3·69	2·95
Hb (g./100 ml.)	5·9	6·8	8·3	10·4	9·3
P.C.V. (%)	17·0	19·0	30·0	34·0	30·0

The patient ate well and had no soreness of the tongue during any of the experimental periods, but notable improvement in strength and colour was observed in the third period.

Comment.—Vitamin B_{12} instilled into a washed segment of intestine, either with or without gastric juice, was not effectively absorbed. The small reticulocytosis observed in the first and second periods was no greater than might have been observed from the oral administration of 80 µg. of vitamin B_{12}. The response to injected vitamin B_{12} was better than expectation.

Not much reliance can be put on the negative results of these intubation experiments. The segment of intestine may have been too small or sited in an area unsuitable for absorption of vitamin B_{12}. Moreover, the protection against contact with intestinal contents was anything but complete.

Oral Administration of Vitamin B_{12} after Partial Sterilization of the Intestine

The object of this experiment was to determine whether vitamin B_{12} would be effectively absorbed if intestinal bacteria which might take up the vitamin were destroyed.

Case 404

A coal-screener aged 56 had pernicious anaemia without neurological involvement. His diet had been satisfactory. During a control period of 12 days the reticulocytes did not exceed 1% and the red cells fell from 1,700,000 to 1,260,000 per c.mm. He was transfused with blood of a different but compatible group so that his own cells could be enumerated. The next day the total count was 1,730,000.

In the first period intestinal antiseptics were given as follows:

1st day: Phthalylsulphathiazole 4 g., six times.
2nd day: Phthalylsulphathiazole 2 g., six times; also "aureomycin" 0.75 g., four times.
3rd day: Same as second, with dihydrostreptomycin 1 g., four times.
4th, 5th, and 6th days: All three drugs as on third day.

Bacteriological examination (Dr. C. A. Green) showed that *Bact. coli* had disappeared from the stools by the third day and cocci by the fifth day. Yeasts persisted even up to the last examination on the seventh day. On the evening of the fifth day the patient received orally 80 µg. of vitamin B_{12}. There was neither reticulocytosis nor increase of red blood cells (Fig. 4).

In the second period 80 µg. of vitamin B_{12} with 500 ml. of gastric juice was given at 7.30 p.m. No food was given for four hours before or after the mixture. The reticulocytes rose to 15.8% on the sixth day. Changes in blood counts were as follows:

	Second Period			
Day:	0	5	10	15
R.B.C. (mills./c.mm.)	1·34	1·51	2·13	2·16
Hb (g./100 ml.)	5·3	5·9	7·4	7·7
P.C.V. (%)	16·0	20·0	24·0	23·0

In the third period 80 µg. of vitamin B_{12} was injected. There was another reticulocytosis, reaching 17.2% on the fifth day. Changes in counts were as follows:

	Third Period			
Day:	0	5	10	15
R.B.C. (mills./c.mm.)	2·16	2·24	3·21	3·70
Hb (g./100 ml.)	7·7	8·0	9·3	10·8
P.C.V. (%)	23·0	24·0	33·0	37·0

Comment.—Preliminary partial sterilization of the intestine did not permit absorption of vitamin B_{12} given orally. The rise of red blood cells in 15 days after giving 80 µg. with 500 ml. of gastric juice was rather less than that expected from the injection of 5 µg. The response to the injected dose of 80 µg. was almost equal to that expected from 40 µg. Thus the oral-dose/injection-dose ratio was probably more than 8 : 1.

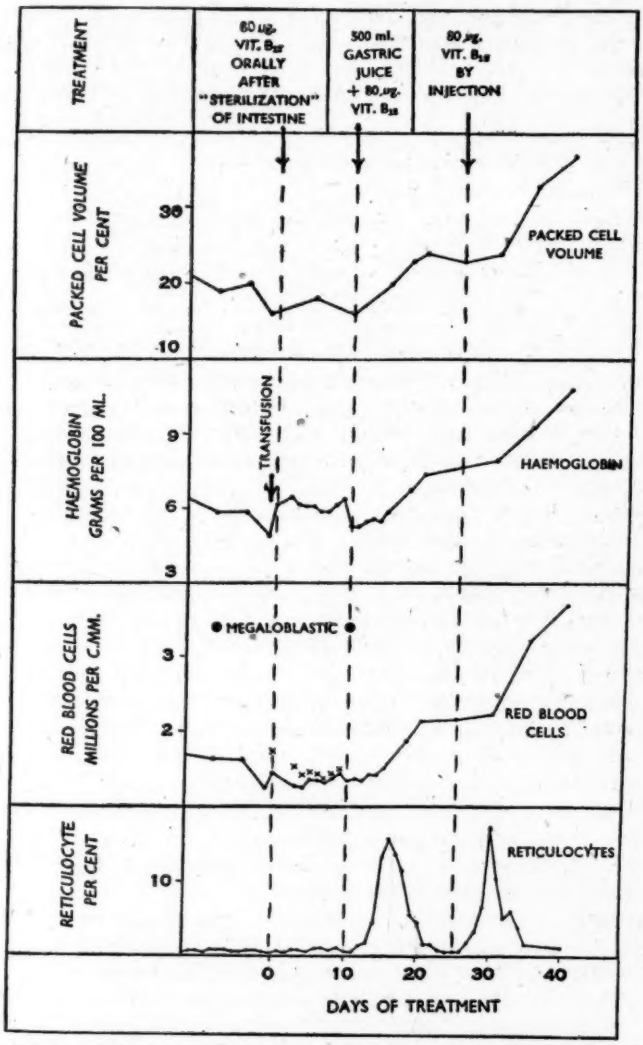


FIG. 4.—Case 404. Showing that 80 μg. of vitamin B_{12} administered orally after partial sterilization of the intestine did not lead to any reticulocytosis or increase of red blood cells. Thereafter the same dose of vitamin B_{12} given with gastric juice produced a response rather less than that expected from an injection of 5 μg. The injection of 80 μg. of vitamin B_{12} was followed by a response almost equal to that expected from 40 μg. (In the section for red blood cells the crosses represent the total count including transfused cells, whereas the continuous line represents the patient's own cells, the donor's cells have been separated by differential agglutination.)

Discussion

Results in Case 401 suggest that there was little, if any, absorption of vitamin B_{12} from the buccal mucosa. Negative results are also reported by Erf and Wimer (1949).

These negative findings and our failure on four occasions to procure effective absorption from a washed isolated segment of intestine lend no support to the idea that vitamin B_{12} given via the alimentary tract might prove effective if contact with intestinal juice were prevented.

The intubation experiments were, however, not altogether satisfactory (see Cases 402 and 403). In another type of experiment an attempt was made to destroy intestinal bacteria which might otherwise take up orally administered vitamin B_{12} and render it unavailable to the host. Using phthalylsulphathiazole, aureomycin, and dihydrostreptomycin, we succeeded in sterilizing the stools except for yeasts. The small intestine was presumably equally sterile. Even so, the administration of 80 μg of vitamin B_{12} orally was without effect.

Moreover, in microbiological tests we showed that "pernicious anaemia" intestinal juice did not destroy added vitamin B_{12}, in the presence either of "pernicious anaemia" or normal gastric juice (Ungley and Cuthbertson, 1950—Paper V of this series, to be published).

The results reported here are negative but not conclusive. They do not support, but neither do they entirely rule out, the hypothesis that Castle's intrinsic factor acts by protecting vitamin B_{12} from destruction in the alimentary tract. Further work is in progress.

Summary and Conclusions

Efforts were made to determine whether vitamin B_{12} would be effectively absorbed if the possibly destructive action of intestinal juice could be reduced or avoided.

Application of 5 μg. daily to the buccal mucosa gave a negative response in a patient who subsequently responded to the same quantity of vitamin B_{12} given with gastric juice.

In four experiments in two patients the instillation of vitamin B_{12} with or without gastric juice into a washed segment of intestine isolated between the two balloons of a Miller-Abbott tube led to negative or trivial responses. In each case the subsequent administration of vitamin B_{12} by injection or orally with gastric juice was effective.

Even after preliminary partial sterilization of the intestine with aureomycin and other drugs the oral administration of 80 μg. of vitamin B_{12} was ineffective. The patient subsequently responded to the same dose of vitamin B_{12} given with gastric juice.

These negative findings are against, but do not entirely exclude, the possibility that Castle's intrinsic factor acts by protecting vitamin B_{12} from destruction in the gastro-intestinal tract.

ADDENDUM.—Since these papers were submitted additional evidence on the effect of orally administered vitamin B_{12} and the role of Castle's intrinsic factor has been reviewed by Dr. Byron E. Hall (*British Medical Journal*, September 9, 1950, p. 585).

I am grateful to the medical, nursing, and lay staff of the hospital and medical school and to many general practitioners for their co-operation. I have to thank Dr. L. W. Carstairs for intubating the small intestine and Dr. R. B. Thompson for marrow biopsies. Special thanks are due to students and others who donated gastric juice. The dental appliance used in Case 401 was constructed with the kind co-operation of Professor John Boyes and Mr. H. G. Hanley, L.D.S., of the Dental School, King's College, University of Durham. Dr. E. Lester Smith, of the Research Division of Glaxo Laboratories, Ltd., Greenford, supplied the crystalline vitamins B_{12} and $B_{12}c$ and also the vitamin B_{12} concentrate used in these investigations. Dr. W. F. J. Cuthbertson, also of Glaxo Laboratories, was responsible for all the microbiological assays.

BIBLIOGRAPHY

Berk, L., Castle, W. B., Welch, A. D., Heinle, R. W., Anker, R., and Epstein, M. (1948). *New Engl. J. Med.*, **239**, 911.
—— Denny-Brown, D., Finland, M., and Castle, W. B. (1948). Ibid., **239**, 328
Bethell, F. H., Meyers, M. C., and Neligh, R. B. (1948). *J. Lab. clin. Med.*, **33**, 1477.
Callender, S. T. E., Mallett, B. J., Spray, G. H., and Shaw, G. E. (1949). *Lancet*, **2**, 57.
Campbell, D. C., Hall, B. E., and Morgan, E. H. (1949). *J. Lab. clin. Med.*, **34**, 1590.
Cuthbertson, W. F. J. (1949). *Biochem. J.*, **44**, Proc. v.
Dyke, W. J. C., Hind, H. G., Riding, D., and Shaw, G. E. (1950). *Lancet*, **1**, 486.
Erf, L. A., and Wimer, B. (1949). *Blood*, **4**, 857.
Fouts, P. J., Helmer, O. M., and Zerfas, L. G. (1935). *Ann. intern. Med.*, **8**, 790.
Girdwood, R. H. (1950). *Lancet*, **1**, 594.
Goldhamer, S. M. (1936). *Amer. J. med. Sci.*, **191**, 405.
Hall, B. E., Morgan, E. H., and Campbell, D. C. (1949). *Proc. Mayo Clin.*, **24**, 99.
Minot, G. R., and Castle, W. B. (1935). *Lancet*, **2**, 320.
Reimann, F., and Fritsch, F. (1934). *Z. klin. Med.*, **126**, 469.
Smith, E. L. (1950). *Proc. R. Soc. Med.*, **43**, 535.
Spies, T. D., Stone, R. E., Garcia Lopez, G., Milanes, F., Lopez Toca, R., and Aramburu, T. (1949). *Lancet*, **2**, 454.
Ternberg, J. L., and Eakin, R. E. (1949). *J. Amer. chem. Soc.*, **71**, 3858.
Ungley, C. C. (1949a). *British Medical Journal*, **2**, 1370.
—— (1949b). *Brain*, **72**, 382.
—— (1950). *Proc. R. Soc. Med.*, **43**, 537.
West, R. (1948). *Science*, **107**, 398.
—— (1949). Paper read at a meeting at Atlantic City, May 3, 1949. Cited by Erf and Wimer (1949).

ACUTE INTUSSUSCEPTION IN CHILDHOOD

BY

Sir JAMES SPENCE, M.D., F.R.C.P.

AND

DONALD COURT, M.D., M.R.C.P.

(From the Children's Department, Royal Victoria Infirmary, Newcastle-upon-Tyne)

This is a sequel to the account of 100 cases of acute intussusception in children given by Morrison and Court (1948). That study revealed the relationship between the delay in reaching a diagnosis and the outcome of the disease, and the parts played by the parents and the family doctor in the process. Although the risk of death increased sharply when intussusception had been present for more than two days, a considerable number of affected children failed to reach hospital within this favourable period. Yet almost every child had been seen by the family doctor before the second day was over. These facts together suggest that the illness was in most cases intense enough to alarm the parents but that in many it failed at this stage to provide the doctor with sufficient evidence for diagnosis. Knowing the difficulties of diagnosis, Morrison and Court paid special attention to the clinical events on the first and second days of the illness. They described these in detail and time-sequence, and asked practitioners to send suspected children to hospital as soon as their suspicions were aroused.

In the three years following the initial study we have seen another 139 children with acute intussusception. With this further experience we return again to the significance of early diagnosis, and comment briefly on the improvement that has occurred and the reasons for it. We attempt also to set this problem in its right perspective. During the six years of this survey the average number of children with intussusception seen by any practitioner in that period was only one, and, although a small number saw more than one in six years, many doctors saw none at all. How, then, shall a family doctor maintain his diagnostic skill with this infrequent contact? The facts and suggestions given below may help to answer these questions.

TABLE I.—*A Comparison of Mortality in 177 Infants with Intussusception Admitted Before and 62 Admitted After the 48th Hour of the Disease*

Year	All Cases			Under 48 Hours			Over 48 Hours		
	No.	Deaths	Death Rate %	No.	Deaths	Death Rate %	No.	Deaths	Death Rate %
1944 ..	29	4	14	14	1		15	3	20
1945 ..	25	2	8	18	—		7	2	28
1946 ..	46	4	9	32	2		14	2	14
1947 ..	49	2	4	38	1		11	1	9
1948 ..	40	3	7	31	—		9	3	20
1949 ..	50	2	4	44	2		6	—	
All years	239	17	7	177	6	3·4	62	11	17·8

Table I shows the mortality in the entire group of 239 children admitted to one hospital from a wide area. It reveals a number of interesting differences between those admitted before and those after 48 hours. First, a fall in the death rate from 14% in 1944 to 4% in 1949. Yet over the six years the death rate for children admitted within 48 hours has not deviated significantly from 3–4%, and of those admitted after 48 hours from 18%. It is still, therefore, of first importance that children with this disease should be in hospital well within 48 hours of the onset of symptoms. A larger number of children were treated in the 1947–9 period, and there has been a gratifying increase in the percentage reaching hospital in the first two days of the illness. This percentage rose from 48 in 1944 to 88 in 1949—an increase which is statistically significant (Table II).

TABLE II.—*The Proportion of 239 Cases of Acute Intussusception Admitted to Hospital Within 48 Hours of Onset*

	1944	1945	1946	1947	1948	1949
% Admitted within 48 hours	48	72	70	77	78	88
		64			81	

Differences in the anatomical types of intussusception have been difficult to measure consistently owing to a lack in some cases of a precise indication of the starting-point. If there has been any change in the first three years it has been a slight increase in the small-bowel invaginations of the ileo-ileocolic variety, while the incidence of pure ileo-ileal intussusception has remained the same throughout. The general paediatric care and surgical technique, too, were unaltered in the second period. A group of surgeons have shared the work, and there has been no attempt to limit this experience to one or two people. Pre-operative resuscitation with plasma has been the rule in almost every child.

In view of these facts the fall in mortality can be primarily attributed to the increasing number reaching hospital within 48 hours, and therefore to the skill of the family doctors concerned.

We have wondered how this earlier recognition of the disease has come about, as intussusception is not common, and most doctors' memories will not be refreshed by frequent contact with the disease.

Interest in the exact incidence of the disease within a community, and in the chance of a doctor's seeing it, led us to trace every child with acute intussusception resident within the City of Newcastle-upon-Tyne during the six years covered by our review. There were 127 such children admitted for treatment to a hospital or nursing-home within the city. The average annual number of births over the period was 5,600, so the incidence of intussusception was 3.8 per 1,000 births, or about 1 in 250 births. The yearly variation was considerable and is set out in Table III.

TABLE III.—*Annual Incidence of Acute Intussusception in Newcastle-upon-Tyne, 1944 to 1949*

	1944	1945	1946	1947	1948	1949	All Years
No. ..	13	13	14	30	20	37	127

During this period the number of doctors resident and practising in Newcastle-upon-Tyne did not vary significantly from 120 in each year. The way in which the 127 children with acute intussusception were distributed among these doctors is shown in Table IV. This gives an average of one case to a single practitioner every six years. Yet during this period 42% of the practitioners did not see the disease at all and a further 36% saw it only once; at the other end of the scale a small group of 27 doctors, 22% of the total, saw 83 cases between them, or 65% of all the affected children in the city. There is therefore no constant pattern in the distribution of this disease within the experience of the urban family doctor, though the majority are not likely to see more than one affected child every six years—that is, 6 or 7 in a professional lifetime.

How, then, has this earlier recognition come about? The article by Morrison and Court may have been noticed

TABLE IV.—*Distribution of 127 Children with Acute Intussusception Among 121 Family Doctors in Newcastle-upon-Tyne, From 1944 to 1949*

Cases per Doctor	No. of Doctors	Total Cases
0	50*	0
1	44	44
2	12	24
3	8	24
4	4	16
5	1	5
6	1	6
7	0	0
8	1	8
Total	121	127

* Estimated from the average number of doctors practising in Newcastle-upon-Tyne during the survey period.

by some practitioners. The main facts were also presented to a well-attended local meeting of the Newcastle and Northern Counties Medical Society. But a new influence has been used in the letters to doctors when the children were discharged from hospital. These have been worded in the last few years with the need for early admission in mind. When the doctor's suspicions of the disease had been quickly aroused and the child reached hospital in good time, confirmation alone was required to complete the happy story. When, however, diagnostic hesitation lasted beyond the second day, the writers of the discharge letters have ventured to discuss those points in the history which might have suggested earlier diagnosis and have led to earlier admission if their significance had been recognized.

As a result of conferences with practitioners we feel that the discharge letter, or a telephone conversation, should usefully go beyond the mere statement of what has been done in hospital, since it is concerned with the fate of a particular person for whom the doctor is responsible. The letter (or the conversation) is an instrument of postgraduate education and commands more interest and attention among practitioners than comprehensive reviews of the subject in journals. Moreover, this exchange is a two-way process of education: it helps the hospital doctor to appreciate the difficulties of practice, from which he may learn what sort of letters to write.

Whatever the full explanation may be, we suspect that these letters, the contents of which would be extended to partners and colleagues by the inevitable discussion among doctors of the unusual or exciting case, may have assisted general practitioners in the North-east to make a notable contribution to the better management of acute intussusception. In any case we are grateful for the facts and offer our thanks to all doctors concerned, both in the home and in the hospital.

Our thanks are due to Mr. H. Campbell, of the Nuffield Department of Industrial Health, for his expert comments on the figures presented in this paper.

REFERENCE

Morrison, B., and Court, D. (1948). *British Medical Journal*, **1**, 776.

A report entitled "Towards the Better Care of the Elderly" has been issued by the Public Health Department, Salford. The report, which has an introductory note by Lord Amulree commending the care of the elderly in their own homes, is an account of two informal conferences, sponsored by the local health department, which were held at Salford this year on May 4 and 5. The first conference dealt with the medical aspects of the care of the aged, and the second with the co-operation of home and hospital in this task. A limited number of copies of the report may be obtained, free of charge, on application to the Medical Officer of Health, Health Department, 143, Regent Street, Salford, 5.

ACTIVITY IN ADVANCING YEARS*

BY

MARJORY W. WARREN, M.R.C.S., L.R.C.P.

Consulting Physician to the Geriatric Unit, and Deputy Medical Director, West Middlesex Hospital, Isleworth, Middlesex

Full health, and with it usefulness and happiness, depends upon activity of mind and body. This applies equally to all age groups, though the amount of mental and physical work which can be undertaken at different ages and by different persons must vary widely, even among healthy individuals. The elderly are no exception to this rule, and the subject of activity is closely associated with modern ideas of their treatment, which embrace psychological and physical methods. In order to strengthen my arguments for retaining or obtaining the maximum activity amongst them it may perhaps be profitable to consider briefly first the results of inactivity both to the individual and to the community, and then to discuss therapeutic measures (medical and social) against such a background.

Anatomically and physiologically, man has been designed for an active existence in the upright or vertical position, and any grave departure from such, for any appreciable length of time, inevitably brings troubles, both mental and physical. Anyone who has inherited patients who have been bedridden for a long time will readily appreciate the picture here described.

Effects of Inactivity on the Individual

Confined to bed, most patients develop rarefaction of bone, stiffness of soft tissues, and contractures. Muscles atrophy, tendons shorten, and limbs assume malpositions varying with circumstances. The type and degree of contracture will depend upon the position in bed. When propped up for long periods of time flexion of hips and knees is almost inevitable. Feet assume a varus, valgus, or equino-varus position, according to the physical disability, the mental state, and the condition of the bedclothes. The elderly when nursed sitting in bed show a great tendency to keep the upper limbs adducted to the trunk in a position of flexion. This results in stiffness and contractures of shoulders and elbows, and is always more marked in the left upper limb with right-handed persons. Also there is a tendency towards some degree of fixed flexion of the head on the chest—often in minor degrees only and therefore not easily noticed when the person is propped up. Such contractures and stiffness lead to difficulties in changing patients' positions in bed and hence lead to the development of pressure sores.

With lowered metabolism, reduced body needs, and the absence of all exercise and voluntary movement, obesity often follows. Such obesity, which is a well-recognized feature in these conditions, is frequently aggravated by the patient's inclination to eat between meals (often of carbohydrate foods), and shows earliest in the anterior abdominal wall. This additional deposit of fat adds another factor to the difficulty of movement in bed, and indeed often prevents a patient from sitting up. It also affects the heart, as such general increases tend to infiltrate the myocardium and so reduce normal cardiac efficiency. Overweight and immobile, such patients show a reduced respiratory excursion and develop signs of

*Read in opening a discussion in the Section of Geriatrics at the Annual Meeting of the British Medical Association, Liverpool, 1950.

basal congestion which are potential sources of active pulmonary infection.

Lack of exercise produces a sluggish bowel action, with resulting constipation. In passing, I would draw attention to the fact that much of the so-called incontinence of faeces is in reality retention of faeces with overflow—a condition not sufficiently recognized. On the nervous and psychological side, such conditions soon produce a degree of mental apathy, especially among those who are less erudite or who, by reason of poor sight and/or poor hearing, are somewhat isolated from their fellows.

Such apathy produces two main results: (1) irregular sleep, with a tendency to sleep between meals by day, and a failure to sleep well at night; and (2) laziness, resulting in incontinence of urine, which further adds to the difficulty of preventing pressure sores. Occasionally, instead of incontinence of urine, retention occurs. This is usually found in men—often in those who have a mild degree of prostatic enlargement. I have, however, met a few such cases in women.

The last case was in an old woman aged 90 who developed retention of urine when put to bed at home following a fractured right humerus. On admission she was in great discomfort with a grossly distended bladder. In spite of all encouragement she could pass only a few ounces of urine normally. Catheterization undertaken slowly over a period of several hours resulted in withdrawal of 5¼ pints (3.1 litres) of urine which showed no abnormal constituents and was sterile on culture. She had a small sessile urethral caruncle, which I do not think was in any way responsible. She was allowed up in a chair daily and at the end of a week normal micturition was re-established.

Effects of Inactivity on the Community

Failure to retain or obtain the fullest possible activity, independence, and useful work amongst the elderly will inevitably lower the general standard of health. With increasing numbers of elderly persons in our population it is obvious that as many as possible must be helped to remain as active members. The more invalids or bed-fast patients there are the greater the burden will be on personnel of all kinds engaged in looking after them and the greater will be the financial strain on the country.

It is obvious, then, that all must play their part in helping the elderly to remain active and retain their full independence—by providing domiciliary service as soon as it is needed, along with recreational interests—and it is certain that the first call should be to the relatives and friends.

There must, I feel, be general agreement on the advisability of maintaining or restoring activity even if there is divergence of opinion on methods, and I therefore propose to discuss the subject from three angles: (1) Conditions relating to a maintenance of personal independence, with or without useful work. (2) Therapeutic methods necessary to bring about a return of useful function and a measure of personal independence where this has been lost. (3) Conditions required for creating and maintaining optimum morale.

Maintenance of personal independence with or without useful work depends upon the attitude of mind of both the individual and those around him, and the patient's medical and social condition.

If the mental attitude of those around an elderly person favours inactivity, or they are quite unaware of the methods by which activity and interest can be maintained, then, indeed, unless help is given, he will become inactive and an unnecessary burden to himself and the community. Overindulgent relatives often persuade an elderly person to take more and more rest and to do less and less; at the other extreme we have the inattentive people who offer nothing to the aged, who in turn rebel and demand everything.

Patients who develop increasing arthritis, considerable cardiac failure, pernicious anaemia, or a mild cerebrovascular catastrophe all need treatment; but these conditions are not infrequently overlooked in the early stages and consequently result in long periods of inactivity.

Finally, an elderly person whose living conditions include an outside toilet, accommodation on the third or fourth floor, or no domestic help may well give up the unequal struggle and demand full service.

It is obvious that such psychological, medical, and social conditions call for full preventive measures. These measures include, in addition to education of the public when needed, full medical treatment when required and use of all domiciliary services which are available, and an increase where these are insufficient.

Treatment

To provide a well-run medical service for the elderly the importance of activity must be well understood, and methods must be fully implemented to ensure it.

Without due care inactivity is apt to follow any illness (medical or surgical) which necessitates a period of time in bed. It therefore behoves all those concerned to regard such a period of rest in bed as a "danger period." With considerable years of personal experience, and after reading widely on the subject, I know of no reasons *on age alone* for recommending a long stay in bed. Indeed, I would suggest that, in treating the elderly, rather than deciding how soon they may safely get up, one should consider very carefully whether it is really necessary and wise to put them to bed.

Although any elderly patient may become inactive after a long time in bed, there are certain conditions which particularly predispose to this state: painful feet from any cause; cerebro-arteriosclerosis with some added minor medical or social problem; cerebrovascular accidents; cardiac disease, in failure; arthritis; progressive nervous disease—for example, Parkinsonism; and post-traumatic and post-operative conditions.

Full activity, which must be aimed at in all cases, depends upon psychological and physical fitness, and these are closely interrelated. Without a degree of mental activity physical progress is very slow, and in the absence of physical progress mental activity wanes appreciably. It must therefore be the aim of the physician to get and to maintain a good balance.

In order to ensure the fullest activity and the most complete rehabilitation the following general methods should be adopted: (1) a detailed history of the patient's illness and earliest symptoms and signs must be obtained from him or his relatives or friends; (2) a full clinical examination, including a rectal examination and blood-pressure reading, must be made before starting treatment. Only with these prerequisites can a sound plan be made and detailed treatment arranged. Many diagnoses are missed in the elderly owing to failure to undertake such preliminaries. With as full knowledge of the patient as possible, treatment must be undertaken by a team, and the members of this team must work in complete harmony if full success is to be obtained.

Such a team will usually include:—In the home: a general practitioner; domiciliary services; relatives and friends. In

the hospital: the physician and his medical staff; nursing staff; physiotherapists; occupational therapists; almoner; dietitian, etc. To complete the picture it is necessary that general practitioners and physicians should work together concerning the patient's future.

When treating sick elderly patients the following principles should be adhered to.

1. A patient must be encouraged to retain full independence for his personal needs whenever possible while under treatment—for example, he should wash and feed himself, brush his teeth, comb his hair, and assist in dressing himself. Nothing that a patient can do for himself should be done for him.

2. If his medical condition has diminished his independence or rendered him immobile, then full treatment by means of physiotherapy, occupational therapy, or speech therapy must be arranged to overcome his disabilities.

3. At all times a patient must be encouraged to persevere with treatment, to keep active in every possible way, and to interest himself in his own full recovery and in his surroundings.

4. Exercise should be frequent and for short periods of time, as the elderly tire easily and yet need repetitive treatment.

5. The time allowed up or for exercise should be laid down in detail, as only with such precision can a true assessment of progress or fatigue be measured.

6. Great care should be taken to ensure that conditions are good as regards flooring, sanitation, temperature, light, etc.; that clothes, especially shoes, are comfortable, well-fitting, and warm enough but not too heavy; and that appliances, including prostheses, are correct in every detail. Crutches and sticks particularly should be the right length or walking may be difficult, or even dangerous.

7. Equipment should be provided with a view to giving the maximum help to patients under treatment, and this includes rails overhead and bed-end pulleys, armchairs, wheel-chairs, self-propelling chairs, etc.

8. All medical conditions must be treated in order to avoid general deterioration from one disability hindering progress of another.

Exercise

In most cases well-planned treatment giving successful results does not depend on elaborate apparatus, but on the knowledge of the therapeutic principles involved. In general, massage is to be avoided, as it is time-consuming and of less value than exercise. Exercises should be undertaken by the patient after careful education, and these will give him an interest in his progress. The physiotherapist, where available, should give regular attention to such patients, partly individually and partly as group therapy. Ideally, treatments should be frequent and short—not more than 15 minutes. Where, however, physiotherapists are not able to give all the treatment necessary some members of the nursing staff—and especially, in my experience, the State-enrolled assistant nurses—can be taught to undertake valuable work in this connexion; but, whatever help is available, the overall supervision must remain with the physician and should never be handed over entirely to ancillary staff.

Exercise may be passive or active, and in many instances a combination of the two methods will prove best. All joints need exercise through a full range of movements daily.

Arthritis

In the case of arthritics, where flexion deformities are commonest, an increased range of movement must be aimed at. This can best be undertaken by a series of graded exercises against springs of varying tension with the limbs suspended in slings—Guthrie Smith frame or an improvised modification. I have found that where pain interferes with exercise it is sometimes profitable to give radiant heat immediately before treatment. This can be provided equally well by any of the recognized radiant-heat machines or by an electric heat cradle placed over the affected part. Active movements against resistance improve muscle tone. Movements between fixed points give some measure of range of movement, and should be encouraged for the sake of accuracy.

Much valuable work can be undertaken on these lines either with the patient lying on the bed with all bedclothes removed, or with him sitting on the edge of the bed swinging his legs and thus overcoming flexion deformities of the knees.

When planning suitable exercises it should be remembered that the aim of treatment is to restore full function so that the patient may be independent regarding his personal needs. It is therefore necessary that all exercises should serve this purpose.

Many patients can be more safely nursed sitting in an armchair by day than reclining in bed, where they tend to become less active. Before a patient can walk he can sometimes get about in a self-propelling wheel-chair, which greatly improves his morale.

When a number of patients can be grouped together for such exercise the natural element of competition is often most stimulating. Encouraging a patient to get into his own clothing (and this is much easier for a woman than for a man, because the clothing of the former is much looser) is in itself very good physiotherapy.

Other exercises which are useful include sitting up from a lying-down position, by any means in the first instance and later with the arms folded, contraction and relaxation of abdominal muscles while lying flat on the bed, and regular quadriceps drill. Arthritics should be told that small degrees of flexion deformity of hips and knees are in themselves no absolute bar to walking.

From bed exercises arthritics should proceed to exercises in standing and walking—in the early stages holding on to a rail, and with the help of sticks, crutches, or poles. Sticks should always be provided with a rubber ferrule, and may be ordinary one-legged sticks, or have three or four legs; the latter I have found of great use in my department when a patient feels insecure with an ordinary stick. Crutches are useful where the upper limbs are able to support them, and are sometimes preferred to sticks. When arthritis is mainly confined to the lower limbs, and is especially marked in the lumbo-sacral spine, I have found duralumin poles provided with rubber ferrules at both ends particularly helpful. Poles have a limited use, but when acceptable they are very good, as they overcome the tendency to stoop.

It is important that patients should never be allowed to try to walk until they are able to rise from a sitting position holding on to a rail, but otherwise unaided, and to maintain the erect position correctly balanced.

Hemiplegics

Patients with hemiplegia resulting from a cerebrovascular accident are from a medical point of view one of the most interesting groups to re-educate and guide—and at the same time one of the most neglected. They range from those who are very easy to those who call for the greatest experience, patience, and detailed work.

From the very moment of catastrophe these patients, if they are to do really well, need detailed care and treatment. On the one hand, it is essential to prevent development of stiffness and contractures, particularly of the affected shoulder-joint, and on the other it is necessary to give re-education as early as possible. As soon as

the patient is conscious he must be taught to play an active part in his own re-education, and his activities must be carefully supervised.

Bed exercises in the early stages are followed by exercises while learning to stand, and, later, by practice in walking with a stick and a little assistance, and, finally, by walking with a stick unaided on the flat and then on the stairs.

During the treatment of all these conditions suitable occupational therapy should be provided, and general interest be stimulated by encouraging visiting, reading, conversation with other patients, and by wireless programmes (via headphones and *not* loudspeakers, unless a room can be set aside for such purpose).

If these principles are adhered to then success in treatment will depend upon early and full treatment, attention to detail in an atmosphere of optimism, strength of the team-work, confidence of the patient in the team, and the experience and activity of the physician.

Summary

The results of inactivity both to the individual and to the community are outlined, and an argument is put forward for the maintenance of full activity and independence among the elderly and for their rehabilitation.

Inactivity may be brought about by psychological, physical, or social conditions; preventive measures against these are described.

Medical conditions which particularly predispose to inactivity are enumerated, and principles underlying their management and treatment are discussed. Warning is given that long periods of rest necessitated by illness must be regarded as "danger periods."

Points stressed are: that good results depend on a high standard of medicine, on really good team-work, and on an atmosphere of optimism and activity, combined with the patient's confidence and co-operation in his treatment.

Some suggestions are made with regard to the treatment of arthritics and hemiplegics.

USE OF INTRAVENOUS AMPHETAMINE SULPHATE IN ACUTE BARBITURATE POISONING

BY

J. D. N. NABARRO, M.D., M.R.C.P.

First Assistant, Medical Unit, University College Hospital

The possible use of intravenous amphetamine sulphate in conjunction with other remedies in cases of acute barbiturate poisoning is seldom considered in this country. When Alles (1933) was investigating the pharmacological properties of this drug in dogs under barbiturate anaesthesia he found that the animals often awoke after its injection. Myerson (1940), in a review of the rationale of amphetamine sulphate treatment, mentioned its possible value in counteracting the effects of barbiturate poisoning. Freireich and Landsberg (1946) reported 14 cases of this condition in which the drug was used; but few of these were severe, and the maximum dose employed was 400 mg. Newman and Feldman (1948) have reported a series of cases of poisoning in which massive doses of picrotoxin were used, supplemented in four by amphetamine sulphate. In the treatment of one of their patients who was 135 hours in coma, 14,190 mg. of picrotoxin and 1,950 mg. of amphetamine sulphate were given.

Pharmacological Aspects

Barbiturate poisoning may cause the death of the patient either by depression of the respiratory centre or through the development of bronchopneumonia. The former is more likely to occur with very large doses and with the short-acting derivatives, whereas the latter is associated with prolonged coma. Specific treatment is therefore directed at stimulation of the respiratory centre and hastening the recovery of consciousness. Picrotoxin has an established place in the management of these cases, principally as a stimulant of the respiratory centre. It has much less action on the cerebral cortex, but on account of its convulsant properties must be used with care.

Amphetamine is widely known as a cerebral stimulant, and its power of awakening both men and animals under the influence of various narcotics has often been reported (Reifenstein and Davidoff, 1938; Myerson *et al.*, 1939), although it has been found to increase the death rate in mice after LD50 doses of barbiturate (Chakravarti, 1939). The action of amphetamine on the respiratory centre has been the subject of conflicting reports, and no consistent stimulant action can be demonstrated. In addition to its effect on the central nervous system amphetamine is a powerful sympathomimetic agent. It produces a rise of blood pressure and should therefore be used with care in older patients and hypertensive subjects. Disturbances of cardiac rhythm following its administration have also been reported (Anderson and Scott, 1936; Waud, 1938).

The very large amounts of amphetamine used in Newman and Feldman's case and in that reported below raise the question of the fate of the drug in the body. When given by mouth in normal doses, part is excreted in the urine, in which it may be detected for some days (Beyer and Skinner, 1940; Monroe and Drell, 1947), and the remainder is probably metabolized (Beyer, 1942). There are a few reports in the literature of the results of large doses being taken by patients not under the influence of narcotics. Transient hypertension, excitement, or confusional states have followed the ingestion of amounts up to 450 mg. (Ehrich *et al.*, 1939; Monroe and Drell, 1947). A few deaths have been attributed to the drug, usually after much smaller quantities, and presumably due either to idiosyncrasy (Smith, 1939) or, as in one case, to subarachnoid haemorrhage (Gericke, 1945). The administration of large doses to monkeys has been found to produce toxic degeneration of the nerve cells and perivenous haemorrhages in the meninges (Ehrich *et al.*, 1939).

Case Reports

Over a period of 18 months intravenous amphetamine sulphate has been used, usually in conjunction with other remedies, in the treatment of seven cases of acute barbiturate poisoning. Four were mild cases with coma lasting a few hours, and in three of these picrotoxin seemed more effective in awakening the patient, although the amount of amphetamine used was probably inadequate in the light of subsequent experience. In the fourth, recovery was little accelerated by either drug. The other three cases had points of particular interest and are recorded in more detail.

Case 1

A woman aged 29 was admitted two and a half hours after taking 80 gr. (5.3 g.) of sodium amytal. The stomach was washed out and picrotoxin (100.5 mg. intramuscularly and 115.5 mg. intravenously) was administered over the next 17

hours. In spite of this the patient remained comatose, and tendon reflexes were obtainable for only a few minutes after each injection. During the next 75 minutes 70 mg. of amphetamine sulphate was given intravenously, and after this the patient woke up and spoke. After an hour without treatment she relapsed into coma and 6 mg. of picrotoxin failed to rouse her. Thirty minutes later a further intravenous injection of 10 mg. of amphetamine again woke the patient, and when this was repeated one hour later she became fully conscious and required no more treatment. (This patient was treated in collaboration with Dr. A. G. Spencer.)

This case demonstrates the superiority of amphetamine over picrotoxin as an awakening agent in the later stages of the treatment of a case of severe barbiturate poisoning. Its action in shortening the period of unconsciousness should reduce the risk of bronchopneumonia.

Case 2

An asthmatic patient, aged 54, 24 hours before admission took 2 gr. (0.13 g.) of phenobarbitone and 1½ gr. (0.1 g.) of pentobarbitone sodium, followed while in a drowsy state by a further 9 gr. (0.58 g.) of pentobarbitone sodium. He was unconscious and cyanosed on arrival at hospital, with widespread rhonchi all over his chest and a respiration rate of 25. He was given 20 mg. of amphetamine intravenously, after which he opened his eyes, and a further 10 mg. 45 minutes later restored him to full consciousness.

This was a mild case of barbiturate intoxication, but in view of the patient's pulmonary condition it was essential to terminate the coma as quickly as possible. Amphetamine sulphate in quite small doses proved effective.

Case 3

A man aged 38 took 96 gr. (6.3 g.) of phenobarbitone and was admitted to hospital 31 hours later deeply comatose, with stertorous respirations at a rate of 16 a minute and a blood pressure of 100/68. The pupils were small with poor reaction to light; the corneal and tendon reflexes were sluggish and plantar responses flexor. The stomach was washed out, but only traces of barbiturate were present in the fluid. In the first three hours 180 mg. of amphetamine was given intravenously; the pupils became dilated and fixed, and the coma and blood pressure were unchanged. During the next three hours 69 mg. of picrotoxin was given intravenously and the blood pressure rose to 120/80. For the next 32 hours picrotoxin, 12 mg., and amphetamine, 20 mg., were given every half-hour, the injections being made into a glucose-saline drip every 15 minutes. Muscular twitching appeared and the dose of picrotoxin was reduced to 6 mg.; after a further 13 hours the twitching became more marked and picrotoxin was discontinued.

Over the next five hours amphetamine only was given; the patient's condition deteriorated, his coma became more profound, and respiration was shallower. Picrotoxin was then restarted, and eight hours later the condition had improved and the amphetamine was discontinued to see if this led to any change in the patient's condition; there was no deterioration of either blood pressure or respiration. However, after another four hours vigorous muscle-twitching occurred and the picrotoxin was permanently stopped and amphetamine in 20-mg. doses recommenced. Seventeen hours later, when 116 hours had elapsed since the drug had been taken, the urine for the first time was free from barbiturates. The patient, however, remained deeply comatose; lumbar puncture was performed and a normal cerebrospinal fluid was obtained which did not contain any barbiturate. Twelve hours later the coma lightened, and after another eight hours the patient regained consciousness—137 hours after taking the tablets. Amphetamine was continued in decreasing amount and at lengthening intervals for a further 15 hours.

Over a period of 121 hours the patient received 4,230 mg. of amphetamine sulphate, 1,086 mg. of picrotoxin, and by intravenous drip 8 pints (4.5 litres) of 5% glucose in normal saline, 12 pints (6.8 litres) of 5% glucose in half-normal saline, 14 pints (8 litres) of 5% glucose, and 1 pint (570 ml.) of plasma. He was also given penicillin, vitamins of the B complex, two-hourly inhalations of 5% CO_2 in oxygen, and was frequently turned from side to side. During this prolonged coma the lungs remained completely clear, and great credit must go to the house-physician (Dr. D. A. Hodgson) and the nursing staff for their conscientious care of the patient. He was subsequently transferred to a mental hospital in which he had previously received treatment. His physician noted no change in his mental condition; the only sequelae to the poisoning and its treatment were thromboses in the leg veins into which the drip had been given. Lamson *et al.* (1949) have shown that in some animals the intravenous infusion of glucose potentiates the action of barbiturates; however, no such effect has been reported in humans, though the relationship has not apparently been specifically investigated.

Comment on the Cases

Many of the properties of amphetamine already referred to make it questionable whether the use of this drug in barbiturate poisoning is ever justified. In mice it increases the death rate from large doses of barbiturate. In man it raises the blood pressure and may produce cardiac arrhythmias; some patients show idiosyncrasy to the drug, which may be fatal. It disappears from the body very slowly, partly by an uncertain metabolic process and partly in the urine; hence with these large doses the amount accumulated must be considerable. In monkeys it produces histological changes in the brain cells.

Kempf (1946) has discussed its possible value, and points out that in mild cases there is little to be gained in the ordinary way by awakening the patient rather than letting him "sleep it off." Case 2 represents an exception to this: the patient was an asthmatic, and if his coma had persisted much longer he would probably have developed bronchopneumonia. Amphetamine in quite small doses proved effective, and there is little reason to suppose that such an amount would be dangerous. The use of larger doses in the severer cases requires more justification.

The outcome in Case 3 is unusual. The patient had taken a fatal dose of phenobarbitone, nearly all of which was probably absorbed, and he did not come under treatment until 31 hours after the drug had been ingested. He received large doses of picrotoxin and amphetamine in the course of treatment, and it is important to try to assess what part, if any, they played in his recovery. During the first three hours, when amphetamine was being administered, his condition remained poor, whereas picrotoxin at once stimulated the medullary centres and removed much of the immediate anxiety. Forty-eight hours later, when muscular twitching necessitated a break in picrotoxin therapy, there was definite deterioration despite the continued administration of amphetamine. Newman and Feldman (1948) recommend that picrotoxin should be used until preconvulsive muscular twitchings appear and amphetamine treatment then be started. It seems, however, that picrotoxin may have to be recommenced if the patient's condition is not maintained. In the early stages of this patient's treatment amphetamine had no demonstrable beneficial effect, but it is possible that subsequently it accelerated the recovery of consciousness. The progress of the first case showed this very clearly. No undesirable results seem to have followed the very large amounts of amphetamine administered.

Management of Cases of Acute Barbiturate Poisoning

These cases are not very common, and frequently first come under treatment during the night. The remedies used are often employed in a half-hearted and haphazard fashion. The following programme is outlined for the management of severe cases in deep coma.

1. If there is marked respiratory depression restorative measures should be applied at once. Intravenous picrotoxin, 6 mg., should be given, and if there is no response 12 mg. every 30 minutes. Oxygen administration may be useful, and in extreme cases the use of a mechanical respirator should be considered.

2. When respiration is restored, or in less severe cases immediately on admission, the stomach should be washed out with 16 pints (9 litres) of saline. (The stomach contents should be retained for examination.) Twenty grammes of magnesium sulphate should be left in the stomach.

3. The intravenous administration of picrotoxin, 12 mg. every 30 minutes, should be continued. A careful watch must be kept for twitching of the facial muscles; picrotoxin must be stopped if this occurs, and amphetamine, 20 mg. at similar intervals, should be given. If the coma then deepens, picrotoxin, 6 mg., every 30 minutes should be restarted; otherwise amphetamine should be continued until the patient regains consciousness and for some hours after, in decreasing doses and at lengthening intervals.

4. If the patient shows no response after the first few hours it is desirable to cut down on a leg vein and set up a drip infusion. A plaster cast should be applied to the leg, otherwise as the patient becomes restless serious damage may occur. The analeptic drugs are given into the tubing of the drip. The fluid given should be glucose (5%) in varying concentrations of saline according to the urinary chloride content. The rate of flow must be regulated to maintain a good urinary output without causing any pulmonary oedema.

5. Rectal wash-outs should be done daily in order to remove any barbiturate in the lower bowel.

6. Milk by gastric tube should be given, and probably vitamin-B complex by intramuscular injection as long as a glucose drip is running.

7. To prevent pulmonary infection prophylactic penicillin should be given, also CO_2 and oxygen inhalations every two hours, and the patient should be nursed on his side and turned frequently.

In mild cases in which the patient exhibits spontaneous movements, a stomach wash-out is in many cases all that is needed; but if for any reason rapid awakening is desirable, one or two intravenous injections of 20 mg. of amphetamine at 30-minute intervals may be given. Some patients admitted shortly after the ingestion of the drug may present a deceptive appearance and should be watched carefully, since they may sink deeper into coma.

Summary

Intravenous amphetamine sulphate is a useful ancillary drug in the treatment of acute barbiturate poisoning. In mild cases in which rapid awakening is desirable it is effective and safe. In severe cases it is of little value in the early stages, but it may shorten the duration of coma if given later, particularly when picrotoxin is producing preconvulsive muscular twitchings.

A case is described in which the patient took 96 gr. (6.3 g.) of phenobarbitone 31 hours before admission to hospital. He recovered after 137 hours in coma. Treatment included 4,230 mg. of amphetamine sulphate and 1,086 mg. of picrotoxin.

A programme for the management of cases of acute barbiturate poisoning is outlined.

I have to thank Professor H. P. Himsworth, Dr. E. E. Pochin, Dr. A. Morland, and Dr. J. F. Stokes for permission to report cases under their care, and Professor C. Rimington for examination of specimens for barbiturates.

References

Alles, G. A. (1933). *J. Pharmacol.*, **47**, 339.
Anderson, E. W., and Scott, W. C. M. (1936). *Lancet*, **2**, 1461.
Beyer, K. H. (1942). *J. Pharmacol.*, **76**, 149.
—— and Skinner, J. T. (1940). Ibid., **68**, 419.
Chakravarti, M. (1939). Ibid., **67**, 153.
Ehrich, W. E., Lewy, F. H., and Krumbhaar, E. B. (1939). *Amer. J. med. Sci.*, **198**, 785.
Freireich, A. W., and Landsberg, J. W. (1946). *J. Amer. med. Ass.*, **131**, 661.
Gericke, O. L. (1945). Ibid., **128**, 1098.
Kempf, G. F. (1946). Ibid., **131**, 1170.
Lamson, P. D., Greig, M. E., and Robbins, B. H. (1949). *Science*, **110**, 690.
Monroe, R. R., and Drell, H. J. (1947). *J. Amer. med. Ass.*, **135**, 909.
Myerson, A. (1940). *Amer. J. med. Sci.*, **199**, 729.
—— Loman, J., Rinkel, M., and Lesses, M. F. (1939). *New Engl. J. Med.*, **221**, 1015.
Newman, E. A., and Feldman, M. (1948). *Arch. intern. Med.*, **81**, 690.
Reifenstein, E. C., and Davidoff, E. (1938) *J. Amer. med. Ass.*, **110**, 1811.
Smith, L. C. (1939). Ibid., **113**, 1022.
Waud, S. P. (1938). Ibid., **110**, 206.

PREGNANCY IN A RUDIMENTARY HORN OF A BICORNUATE UTERUS

BY

DOUGLAS LATTO, M.B., Ch.B., M.R.C.O.G.

AND

RICHARD NORMAN, M.R.C.S., L.R.C.P.
D.Obst.R.C.O.G.

(From the Nuffield Department of Obstetrics and Gynaecology, Radcliffe Infirmary, Oxford)

This case of pregnancy in a rudimentary horn is discussed at some length because of the great danger there may be to the patient. Unlike tubal gestation, in which less than 50% rupture and present the classical picture, 90% of the cases of pregnancy in a rudimentary horn rupture, and as this occurs about the sixteenth week the bleeding is profuse. Very little has been written on this subject recently, and the relatively high incidence of the condition is not generally realized.

Pregnancy in a rudimentary horn was first described by Mauriceau and Vassal in 1669. Kehrer in 1900 collected 84 cases from the literature, and Beckmann in 1911 found 146 cases. DeLee and Greenhill (1947) state: "Perhaps 100 cases have been described. Mulsow found reports of only nine cases since 1911." Mulsow (1945) himself, however, said: "With the aid of the librarian of the Iowa State Medical Library at Des Moines, I have been able to review the records of nine cases which have been reported since Beckmann's review in 1911." In the *Index Medicus* for the past 25 years we have found over 40 reported cases: in all probability, therefore, well over 200 cases have now been described.

Case Report

The patient was admitted to the Radcliffe Infirmary on January 15, 1950, complaining of severe abdominal pain of four hours' duration. She had had vague pain in the right iliac fossa for the past week, and had felt sick but had not vomited. Menstruation had been regular until September 16, 1949, since when there had been amenorrhoea. There was very little else of significance in her history except that she had a normal full-term pregnancy in 1946, a spontaneous breech delivery; also she had rather severe hyperemesis in the first three months of this pregnancy.

The patient looked distressed and was obviously very ill, with restlessness and air-hunger. The skin was cold and clammy,

and she had the typical pale waxy appearance indicative of sudden profuse loss of blood. The pulse was rapid and thready, and the blood pressure 70/30. The abdomen was slightly distended and there was extreme tenderness all over it. A soft mass was palpated in the pouch of Douglas. Bimanual examination was unsatisfactory because of the abdominal rigidity and distension. A provisional diagnosis of pregnancy in a ruptured rudimentary horn was made. Other conditions considered in the differential diagnosis were ruptured ectopic gestation and rupture of and haemorrhage from an ovarian cyst. Operation was decided upon soon after the patient had begun to respond to the initial shock therapy—warmth, ¼ gr. (11 mg.) of morphine, and blood transfusion (Group A, Rh-negative).

Under general gas, oxygen, and ether anaesthesia the abdomen was opened through a paramedian subumbilical incision. The abdominal cavity contained about four pints (2.27 litres) of blood. The foetus could be seen inside the intact amnion and was attached to the rudimentary horn. The normal horn was about the size of a 10-weeks pregnancy. The foetus and rudimentary horn and tube were removed leaving the ovary. The round ligament and ovary were then stitched to the normal horn for support and to cover the raw area. The remainder of the blood was removed from the peritoneal cavity and one pint (570 ml.) of saline inserted. The abdomen was closed in layers. The patient's condition was satisfactory at the end of the operation and the blood pressure was 100/60. She made an uninterrupted recovery (a pyelogram showed the renal tract to be normal).

On February 27 a blood transfusion follow-up showed: Group A, Rh-negative; complete anti-D antibodies, titre 1:2; incomplete anti-D antibodies, titre 1:2; haemoglobin, 92% (13.5 g.).

Discussion

It is said that the part of the rudimentary horn attached to the normal horn usually has no canal. Piquand (1910) states that there is a canal in only 15% of cases, but this is observed only when the uterus approaches the bicornis-unicollis type.

One may read in any textbook that the spermatozoon ascends the normal horn and Fallopian tube and crosses the peritoneal cavity to fertilize the ovum. The fertilized ovum then gets into the rudimentary horn. This explanation seems untenable, and we are of the opinion that the rudimentary horn is not occluded until after pregnancy in most cases, for the following reasons:

1. It is improbable that one spermatozoon can fertilize an ovum, and it is very unlikely that a sufficient number of spermatozoa can find their way across the peritoneal cavity. A large number of spermatozoa are required to fertilize an ovum because of the hyaluronidase content required to "dissolve" off the corona radiata surrounding the ovum. A man with 10 million spermatozoa per ml. is virtually incapable of becoming a father because somewhere in the region of 50–100 million spermatozoa per ml. is thought necessary.

2. The corpus luteum is usually found on the same side as the rudimentary horn. On rare occasions it has been reported that the corpus luteum was found on the opposite side, the fertilized ovum then crossing the peritoneal cavity (internal migration of the ovum cannot always be excluded in these cases). With prolapse of the ovaries the tubes may be almost lying side by side, which may account for a few of these anomalies. It is well known that an ovum may cross the peritoneal cavity as in the cases of pregnancy reported after previous contralateral removal of tube and ovary.

3. Many cases show a canalization of the distal end of the rudimentary horn, and this canal leads into the cavity of the normal horn, as illustrated by Munro Kerr and Chassar Moir (1949). The canal was easily demonstrated in the case described.

4. The microscopical examination of the canal is almost invariably made after a pregnancy has occurred. The canal could easily have been occluded by the tissues reacting to the advancing syncytium and by the fibrin laid down in the small haemorrhages. To a less degree a similar occlusion can be found in the Fallopian tube in ectopic gestation.

5. The cervix uteri in comparison is occasionally completely occluded during pregnancy in conglutination of the cervix, which may happen after trauma and mild infection at a previous pregnancy. The canal may be so obliterated that no evidence of it can be found, but, as in the case of the rudimentary horn, the spermatozoa must have got in before the canal was occluded.

6. A case described by Banister (1937) lends further support to our contention. In this case an ovarian cyst was thought to be complicating pregnancy. At laparotomy a four-months foetus was found in a normal horn and a three-months foetus in a rudimentary horn. If this is a case of superfoetation or superfecundation it is possible that the pregnancy in the normal horn occurred first. Before the uterine cavity was completely filled the other conception took place. The rudimentary horn was attached near the cervix of the normal horn. (It is possible that the foetus in the rudimentary horn was growing more slowly because of the poor "soil.") The pregnancy in the rudimentary horn was removed and the other pregnancy went to term and resulted in a spontaneous delivery of a normal child.

7. Pregnancy in a rudimentary horn has been shown not to be extremely rare, and if the horn were not canalized one would expect to see more cases of haematometra. Of course it must be admitted that they occasionally do occur, and, furthermore, it has been said that the endometrium in the rudimentary horn is infantile and refractory to hormonal stimulation.

Summary and Conclusions

A case of pregnancy in a rudimentary horn is described and its aetiology discussed.

Pregnancy in a rudimentary horn is more frequently encountered than one is led to believe by many textbooks. We are of the opinion that the theory of transabdominal migration of a spermatozoon is untenable, and that if a patient gets a pregnancy in a rudimentary horn the canal of that horn is patent before pregnancy in almost every case.

References

Banister, J. B. (1937). *Proc. R. Soc. Med.*, **30**, 562.
DeLee, J. B., and Greenhill, J. P. (1947). *Principles and Practice of Obstetrics*, p. 474. Saunders, Philadelphia and London.
Kerr, J. M. M., and Moir, J. C. (1949). *Operative Obstetrics*, p. 446. Baillière, Tindall and Cox, London.
Mauriceau and Vassal. Quoted by Mulsow (1945).
Mulsow, F. W. (1945). *Amer. J. Obstet. Gynec.*, **49**, 773.
Piquand, G. (1910). *Rev. Gynéc. Chir. abdom.*, **15**, 401.

The Society for the Rehabilitation of Disabled and Crippled Children (of India) has issued its first annual report, covering the period March, 1947, to December, 1948, with a postscript on 1949. It is the first time in India that something is being done to provide organized physiotherapy and orthopaedic treatment for children after poliomyelitis, or with spastic paralysis. The Society's out-patient clinic in Bombay is housed in a military hut loaned by the Government of Bombay and equipped by private donors; it is staffed by a number of ex-Army physiotherapeutic technicians and voluntary social workers. Up to the end of September, 1949, about a thousand patients had registered for treatment, over 800 of them poliomyelitis cases.

Medical Memoranda

Larval Conjunctivitis

Although larval conjunctivitis is well recognized in hot climates, it is rarely encountered among white patients. It is of interest, therefore, to describe three cases which occurred among British Service men in Egypt.

Case Reports

Case 1.—An aircraftman was referred to the ophthalmic department with a history that while cleaning a 20-mm. cannon three days previously he felt something enter his left eye. Immediate examination by his colleagues revealed no foreign body. The eye became red and irritable, and watered. On examination the conjunctiva was seen to be inflamed and oedematous. With a loupe several tiny larvae were seen moving in the upper and lower conjunctival fornices and wriggling across the cornea. The larvae were less than 1 mm. long and owing to their small size and transparency were almost invisible to the naked eye. After cocainization seven larvae were removed with pointed conjunctival forceps. The larvae were identified as those of *Oestrus ovis*. Two days later, following irrigations with bland lotions, the patient was symptom-free and the eye normal.

Case 2.—A healthy young soldier was referred to the ophthalmic department complaining of a sudden stabbing pain in the right eye, as if there was a foreign body in it. He had been cleaning an air cleaner from a tank with a mixture of petrol and oil, and he thought that some had entered his eye. On examination conjunctival injection was present and several larvae were seen crawling across the tarsal conjunctiva and moving further into the fornices. The cornea was criss-crossed with multiple superficial abrasions, a result of the larvae being rubbed across the corneal epithelium. Eleven larvae of *Oestrus ovis* were removed. The conjunctival irritation settled down the following day, and the patient was returned to his unit free from symptoms.

Case 3.—An aircraftman felt something fly into and out of his right eye while he was removing an aircraft propeller. The eye became painful and was irrigated several times. He was seen eight hours later, when the upper lid was oedematous, the conjunctiva injected, and the cornea showed superficial abrasions. Several worms were seen moving across the cornea, and thirteen were removed from the conjunctival sac. They were identified as larvae of *Oestrus ovis*. Three days later the conjunctiva was white and the abrasions healed.

Comment

In these cases it may be assumed that the fly deposited its young directly on the conjunctival surface, though *Oestrus ovis* is said to lay its eggs at times while flying, without alighting (Strong, 1942).

Oestrus (bot-fly) is one of the genera of the Oestridae. It is parasitic normally in the nasal passages and sinuses of sheep, and also infects man. Oestridae possess penetrating organs known as ovipositors and can lay their eggs beneath the conjunctiva (Duke-Elder, 1938). Most of the recorded cases have been infections by *Hypoderma bovis*, the larvae of which may penetrate the globe.

Robinson (1949) reported a case of larval conjunctivitis in a naval officer at Malta in whom three larvae of *Oestrus ovis* were found. The greatest number recorded is 77.

Prompt treatment of the condition is advised in order to prevent the serious complications of corneal ulceration and intraocular invasion.

I wish to express my thanks to the Director-General of Medical Services, Royal Air Force, for permission to publish this paper.

J. S. Conway, D.O.M.S.,
Squadron-Leader; Late
Ophthalmic Specialist, Middle East Air Force.

References

Duke-Elder, W. S. (1938). *Textbook of Ophthalmology*, **2**, 1676. London.
Robinson, G. E. (1949). *Brit. J. Ophthal.*, **33**, 259.
Strong, R. P. (1942). *Stitt's Diagnosis, Prevention, and Treatment of Tropical Diseases*, p. 1517. Philadelphia.

Arteriovenous Fistula Complicating an Amputation Stump

The occurrence of an arteriovenous fistula is an unusual complication of an amputation, and was thought to be a sufficient rarity to warrant publication.

Case Report

On December 9, 1948, a man was referred to the Bradford Royal Infirmary complaining of pain in an amputation stump. The following history was obtained.

In 1936, when aged 17, he was involved in a road accident, a heavy vehicle passing over his left leg. An above-knee amputation was performed on the same day. He was subsequently fitted with an artificial limb, which he stated was never very comfortable but did not cause any pain. The stump was quite satisfactory until about a year ago, when he experienced pain accompanied by a throbbing sensation. The pain had increased during the past three months to such a degree that he had to discard his prosthesis for long periods, with resultant loss of earnings. He stated that he had no dyspnoea or palpitation.

On examination the amputation stump was satisfactory in shape and length. Posterior to the scar one could feel a distinct thrill over a pulsatile ill-defined mass coinciding with the heart beat. A loud bruit with systolic accentuation could be heard on auscultation over the mass. The B.P. was 140/98 mm. Hg. The pulse rate was 82, this slowing to 68 on pressure over the femoral artery in the groin. Release of the compression caused the pulse rate to rise to 80. A skiagram of the chest showed the transverse diameter of the heart to be increased, with prominence of the right ventricle. An arteriovenous fistula between the femoral vessels was diagnosed. An arteriogram was attempted with a view to revealing the type of connexion between the affected vessels. This was of little value, but it revealed a tortuous dilated vein in the stump.

He was admitted to the Infirmary on December 30. An incision was made along the medial aspect of the lower end of the stump, curving posteriorly to end below the mass. An irregular saccular pulsatile mass was exposed, the femoral artery entering this proximally. The femoral vein was grossly dilated and was seen to emerge from the mass, while numerous small vessels entered it. The main trunks and smaller vessels were ligated, the fistula excised, and the wound closed with drainage. Recovery was uneventful.

Attempts to demonstrate the vascular communication in the excised mass by radiology failed, but on dissection a well-marked arteriovenous fistula was demonstrated 2½ cm. from the cut ends of the vessels.

Comment

The fistula probably either originated as the result of a mass ligation of the damaged femoral vein and artery or developed from damage to the arterial and venous walls at the time of the original injury. The latter is the probable explanation, in view of the late onset of symptoms.

A. Naylor, Ch.M., M.Sc., F.R.C.S.,
Consultant in Orthopaedic Surgery to the
Bradford Royal Infirmary.

In *British Health Resorts*, the official handbook of the British Health Resorts Association, information is given on the climate and special features of health resorts in Britain and the British Commonwealth. The particular conditions for which patients may be sent to a resort are listed under each one, and full meteorological data are included. The eighth edition of the handbook is obtainable for 4s. 6d. from the association at Bourdon Street, Berkeley Square, London, W.1.

Reviews

HAEMATOLOGY EXPANDS

Disorders of the Blood. Diagnosis: Pathology: Treatment: Technique. By Sir Lionel E. H. Whitby, C.V.O., *M.C.*, M.A., M.D.(Cantab), F.R.C.P., D.P.H., and C. J. C. Britton, M.D.(N.Z.), D.P.H. Sixth edition. (Pp. 759; 12 colour plates and 94 text-figures. £2 2s.) London: J. and A. Churchill. 1950.

Practical Haematology. By J. V. Dacie, M.B., B.S.(Lond.), M.R.C.P.(Lond.). (Pp. 172; 13 illustrations. 10s. 6d.) London: J. and A. Churchill. 1950.

The sixth edition of Whitby and Britton's *Disorders of the Blood* will be sure of a welcome, and haematologists in this country in particular will be grateful to the authors for coping successfully with the Sisyphean task of keeping the book and its readers up to date and maintaining the high reputation of this standard British text. In the present edition the literature is surveyed to the end of 1949. Vitamin B_{12} is adequately treated, but A.C.T.H. is a cloud no bigger than a man's hand, and the names of Hench, Kendall, and Selye are not mentioned. The main changes have been in the fields of coagulation, blood grouping, and haemolytic anaemia, where considerable progress, not to say complication, has occurred. The book now has 759 pages, of which the index occupies over 40. The production is excellent. Some coloured photomicrographs have been added; these are commonly regarded as being more objective than paintings, but they are not so illustrative, and owing to difficulties in focusing rarely reveal all that the observer can see in the cell.

Some five hundred people from all over the world attended the recent international congress on haematology at Cambridge. Although the famous names were a big draw, different topics attracted rather different audiences, and it seems that the subject of blood coagulation and also that of blood grouping, with which is associated the serological study of the haemolytic diseases, have already developed into separate entities. The importance of the former depends on the frequency of thrombosis and embolism, that of the latter on the world-wide development of blood-transfusion services, and neither of them is the exclusive concern of haematologists in the narrow sense. Leukaemia and allied conditions have an enormous literature which merges with that of cancer as a whole. One cannot help wondering how long it is going to be possible to write textbooks of haematology which deal in detail with all these subjects, and whether they will not have to give place to the primer, the separate monograph, and the encyclopaedia. Meantime we are grateful to Whitby and Britton for having made so much learning so easily available to us.

Dr. Dacie's little book is sure of a welcome by haematologists and directors of laboratories. It is based on lectures to students taking the course for the London University Diploma in Clinical Pathology, and it contains descriptions of the routine haematological techniques—including some for the haemolytic and haemorrhagic diseases and for blood grouping, which are relatively new, but which are being increasingly demanded. Methods of staining films are given, but there are no pictures of blood cells. The book should therefore be used in conjunction with a textbook or an atlas. This is an advantage, as it means that the book has been produced at a low price and no one need be afraid of using it on the working bench. A great virtue is that it emphasizes the errors made and the time lost in certain classical haematological procedures. Another writer (Jennings, D., *Lancet*, 1950, 2, 234) has recently asked:

> "Does any haematologist who knows the clinical history, the haemoglobin and the haematocrit reading, and who has a stained blood film in front of him, get any further aid in diagnosis from a red-blood-cell count which is likely to be more than 10% out in a third of cases and more than 20% out in one of twenty cases? Have our patients derived any benefits from these counts, or have millions of hours during the last 30 years been squandered?"

The classification of anaemias by the diameter, volume, and shape of the red cells has made the profession too red-cell conscious, and it is not sufficiently realized that a Price-Jones curve is a research procedure and that an accurate red-cell count is difficult to obtain. Estimation of the haemoglobin and a glance at the film, supplemented if necessary by the haematocrit and E.S.R., are quick and accurate guides which tell us all we need to know about most cases of anaemia. Elaborate procedures such as counting red cells, platelets, and differential white cells should probably be centralized in laboratories where special apparatus and mechanical aids can be installed. There will always be individual preferences over technique, but it is surprising that Dr. Dacie devotes so much space to the estimation of haemoglobin by the methods of Haldane, Sahli, alkaline haematin, and cyanhaematin. Most haematologists now prefer to estimate haemoglobin as oxyhaemoglobin in a grey-wedge visual photometer or a photo-electric colorimeter. Measurement of clot retraction is of no value in diagnosis and should be replaced by measurement of platelets and fibrinogen. Dr. Dacie does not mention the help obtained from a simple hand tally in most forms of counting.

L. J. WITTS.

DIAGNOSTIC RADIOLOGY

Lehrbuch der Röntgendiagnostik. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Lehlinger. Vol. 1, Skelett. Fifth edition. (Pp. 426; 507 illustrations. M. 66.) Stuttgart: Georg Thieme. 1950.

To many diagnostic radiologists Schinz's textbook is a bible, and it is therefore a great pleasure to see this new edition appear after a lapse of twelve years since the last one. It is almost inevitable that some of the contributors should have died during this period. Lysholm, Holz, and Ulrich have gone, and the rest of the old team has been strengthened by the addition of ten new contributors. Nearly all, both old and new, are Swiss and Swedes, mostly from Zurich and Stockholm.

This first part, entitled "Skelett," deals only with some aspects of the skeleton. None the less one gains a fair impression of what is yet to come. The most striking change from the last edition is the greatly increased size of the work. The new edition promises to be over twice as large and will probably be completed in about ten parts. The basic structure of the book remains unchanged; some illustrations have been removed and many new pictures, diagrams, and tables added.

The first 100 pages are on the physical properties of *x* rays as applied to diagnostic radiology, and a new chapter by Brandenberger on structure analysis has been added. The chapter on bone growth and epiphysial development is excellent; it has been much enlarged and new work on this subject has been incorporated. No fewer than 155 well-chosen references are appended to this chapter alone. Although the bibliography has a Continental bias, the main British and American papers are quoted.

The last chapter—on fractures—has been increased from 40 to 200 pages and many good line diagrams have been added. The remaining parts are expected to be published at intervals of roughly six months.

Until now the reader who has no German (or Spanish, for the last edition was translated into that language) has been denied access to this bible of much of the European continent. It is indeed good news to learn that a New York publisher has undertaken the translation into English and that the volume under review will appear in English before the end of the year.

J. W. D. BULL.

ACTINOMYCETES

The Actinomycetes. Their Nature, Occurrence, Activities, and Importance. By Selman A. Waksman, Ph.D. (Pp. 230; 39 figures. $5.) Waltham, Mass.: Chronica Botanica Company. London: Wm. Dawson and Sons. 1950.

Waksman, the discoverer of streptomycin, is a soil microbiologist, and he cultivated *Streptomyces griseus*, the source of this antibiotic, from a sample of soil so long ago as 1916. In a sense we owe to him not only this discovery but that of the newer antibiotics, since they too are derived from organisms of the same genus, and it was he who opened the gate to this fruitful field of exploration. A delightful and apposite quotation from Walt Whitman which prefaces this volume reminds us of the author's primary interest, and of the fact that the soil is the main habitat of the actinomycetes. Indeed, they may form as much as 40% of its total microbial population and play a large part in the breakdown of plant and animal residues. To this beneficent activity may be added on their credit side the formation of antibiotics and at least one useful vitamin (B_{12}) and enzyme (superbiolase). On the other hand, two genera (not, it is now believed, soil inhabitants) are pathogenic to man and animals, and one to plants.

The only chapter in this book having direct application to medicine is that on actinomycosis and related diseases, and this is of interest rather as a historical account and as a guide to classification of pathogenic species than from any clinical point of view. To the microbiologist, on the other hand, the whole book will be of great value as a systematic and authoritative account of these organisms, for the author describes in detail their classification, distribution, morphology, metabolism, and functions. It is well illustrated, largely by photographs, and thoroughly documented.

L. P. GARROD.

MEDICAL PHOTOGRAPHY

An Introduction to Medical Photography. By Josephine Hunt, S.R.N., S.R.C.N., F.I.B.P., F.R.P.S. With a foreword by Sir Cecil Wakeley, K.B.E., C.B., D.Sc., F.R.C.S., F.R.S.Ed., F.R.P.S. (Pp. 243; 87 illustrations, 4 in colour. £1 10s.) London: Staples Press. 1950.

Advanced manuals of photography on the one hand and elementary handbooks on the other are freely—the latter perhaps too freely—available. In her book Miss Hunt has set out to bridge the intervening gap for the student medical photographer, who, it is assumed, will already have a basic knowledge of photography but will know nothing of hospitals.

The author has thirty years of practical experience: the book is a rather conversational distillate of that experience, and it will be of great value to the neophyte. It is not a textbook of medical photography, nor is it intended to be. But it does contain a wealth of good advice on the relations of the photographer (and for that matter any medical auxiliary) with the medical and administrative staff. The chapter on "The Patient" reveals a humanity which is refreshing in these days of centralization.

The book ends with a chapter on cardiography, on which the author is an authority, with many years' experience at King's College Hospital. In the present context it is misplaced; the medical photographer is rarely associated with the subject, and his field to-day is wide enough without it.

ROBERT OLLERENSHAW.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Chemistry and Therapeutics of Synthetic Drugs. By J. W. Keyser, M.Sc., A.R.I.C. (Pp. 458. 42s.) London: George Newnes. 1950.

D.D.T. and Newer Persistent Insecticides. By T. F. West, D.Sc., Ph.D., F.R.I.C., and G. A. Campbell, M.Sc., F.R.I.C. 2nd ed. revised. (Pp. 632. 50s.) London: Chapman and Hall. 1950.

Dental Anatomy and Physiology for Students. By J. Aitchison, B.Sc., L.D.S. 2nd ed. (Pp. 418. 25s.) London: Staples Press. 1950.

Character Analysis. By W. Reich. (Pp. 516. 35s.) London: Vision Press and Peter Nevill. 1950.

Savill's System of Clinical Medicine. Edited by E. C. Warner, M.D., F.R.C.P. 13th ed. (Pp. 1,198. 35s.) London: Edward Arnold. 1950.

Florence Nightingale. By C. Woodham-Smith. (Pp. 615. 15s.) London: Constable. 1950.

The Slender Thread. By D. Baber. (Pp. 256. 9s. 6d.) London: William Heinemann. 1950.

The Sanitary Inspector's Handbook. By H. H. Clay, F.R.San.I., F.I.S.E. 7th ed. (Pp. 565. 25s.) London: H. K. Lewis. 1950.

The Nutritional Improvement of Life. By H. C. Sherman. (Pp. 270. 24s.) London: Geoffrey Cumberlege. 1950.

Brompton Hospital Reports. Volume 18, 1949. (Pp. 221. 12s. 6d.) London: Brompton Hospital. 1950.

Injuries to the Ankle. By J. G. Bonnin, M.B., B.S., F.R.C.S. (Pp. 412. 63s.) London: William Heinemann. 1950.

Technique of Analytical Psychotherapy. By W. Stekel. (Pp. 403. 21s.) Revised edition. London: The Bodley Head. 1950.

Industrial Lung Diseases of Iron and Steel Foundry Workers. An investigation by the Factory Department of the Ministry of Labour and National Service. (Pp. 282. 21s.) London: H.M.S.O. 1950.

New and Nonofficial Remedies. Issued under the direction and supervision of the Council of Pharmacy and Chemistry of the American Medical Association. (Pp. 800. 27s.) London: J. B. Lippincott. 1950.

Electrophysiological Technique. By C. J. Dickinson, B.A., B.Sc. (Pp. 141. 12s. 6d.) London: Electronic Engineering. 1950.

Plant Viruses and Virus Diseases. By F. C. Bawden, M.A., F.R.S. 3rd revised edition. (Pp. 335. $6.) London: William Dawson and Sons, Ltd. Waltham, Mass.: The Chronica Botanica Co. 1950.

Les Dermatoses Allergiques. Edited by A. Tzanck and E. Sidi. (Pp. 438. 1,800 francs.) Paris: Masson. 1950.

Gliedmassenamputationen und Gliederersatz. By W. Marquardt, M.D. (Pp. 192. M. 28.50.) Stuttgart: Wissenschaftliche. 1950.

Bronchus et Pulmo in ihren Klinischen Beziehungen. Edited by A. Wernli-Hässig, M.D. (Pp. 176. 15 Swiss francs unbound, 19 Swiss francs bound.) Basle: S. Karger. 1950.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY OCTOBER 21 1950

EUGENICS AND HEREDITY

The first two occupants of the Galton Chair of Eugenics at University College, London, Karl Pearson and R. A. Fisher, started their careers as mathematicians. The present professor, L. S. Penrose, is the first to be medically qualified; and it is inevitable that his outlook should differ from that of his predecessors. A mathematician will tend to concentrate on the problem of how the numbers of congenitally handicapped members of a population can be diminished in future generations and the numbers of congenitally superior members increased. A physician, while not neglecting this problem, is likely to be at least equally interested in the therapeutics of inborn diseases and abnormalities; and in the paper which Professor Penrose read at the Annual Meeting of the B.M.A. in Liverpool last July, and which is reproduced in the opening pages of this issue, he emphasized this point.

Many readers will think that he has underestimated the possibilities of preventive eugenics—that is to say, the elimination of injurious genes. But a careful perusal of his article will show that his statement is correct. There are abnormalities in which about half the children of affected persons resemble their parents. But, on the one hand, such clear-cut dominance is quite rare, and, on the other, such injurious genes are constantly reappearing by mutation. For example, in Sjögren's recent study of blindness due to congenital microphthalmia in Sweden, only 12 of the 65 children investigated had one parent similarly affected. Had these parents been prevented from breeding, these 12 children, and 18 normal ones, would not have been born. While preventive eugenics could prevent the birth of a few thousand abnormals in each generation, the conditions to which it could be effectively applied are all rare; and such measures, even if rigorously carried out, would not succeed, in Professor Penrose's words, in "making any appreciable change in the genetical composition of the population." There is certainly, as he points out, a genetical element in the causation of such common diseases as diabetes and mammary cancer; and unfortunately the number of patients with either of these two diseases is much larger than the number suffering from all the comparatively rare complaints with straightforward dominant inheritance. This does not mean that preventive eugenics are worthless. It does mean that, with our present knowledge, they cannot achieve very much.

On the other hand, Professor Penrose was, if anything, over-cautious in his claims for the therapeutic importance of human genetics. In very many cases, including diabetes and gout, there is good evidence that what is genetically determined is not the disease but the diathesis. The rapid progress of biochemical genetics makes it entirely possible that such inborn diatheses may be detectable long before the appearance of overt symptoms, and that dietary moderation, and perhaps therapeutic measures as yet unexplored, may postpone, or even completely prevent, the onset of manifest disease. We all have our weak points: it may be that the main function of medical genetics will be to reveal them before they have betrayed us. But Professor Penrose has done a service in emphasizing that because a disease is congenital or hereditary it is not incurable. In some cases, as with neonatal jaundice, the cure may be permanent. In others, such as methaemoglobinaemia and the de Toni-Fanconi syndrome, treatment may have to be continued indefinitely. Those who regard the treatment of such conditions as weakening the human stock should logically deprive congenital myopics of their spectacles and trust to their selective elimination by motor traffic.

It is, however, conceivable that one of the main contributions of human genetics to medical progress will be its influence on the development of physiology and biochemistry. It is not perhaps always remembered that cystine was first produced by a congenital cystinuric, and that this unfortunate victim of stone in the bladder played a substantial if indirect part in saving the lives of sufferers from arsenic poisoning treated with British anti-lewisite a century after his death. At the present time a study of what can fairly be called the congenital diseases of the mould *Neurospora* is elucidating the intermediary metabolism of the amino-acids. It is almost certain that when we understand why phenylketonuria—which is due to a block in phenyl-alanine metabolism affecting the whole body—profoundly disturbs brain function without affecting that of other organs, we shall have enough clues to the peculiarities of brain metabolism to open a new chapter in pharmacology. When we understand just what has gone wrong with bone metabolism in the osteopsathyrosis associated with blue sclerotics, we may be able to speed up the healing of fractures. A genetically determined disease, like any other, may be regarded as an experiment performed by nature on a patient. But it differs from most infectious diseases in being a far more precise experiment. Whereas tuberculosis can kill by damaging almost any organ in the body, a disease of the type studied by geneticists is due to an abnormality of one

or two genes in each cell nucleus, the genes playing the same sort of parts in the physiology of the cell as organs do in that of the body as a whole. Each such disease is a disturbance of a particular function, and may be compared with a malady such as Graves's or Addison's disease which has not only demonstrated the function of a particular organ but led to the discoveries of substances as valuable as thyroxine and "cortisone."

The close connexion between genetics and obstetrics was mentioned by Professor Penrose. Strictly speaking, the influence of the mother on the foetus during pregnancy should be regarded as environmental rather than hereditary. Nevertheless, the geneticist must study it very carefully, and can give invaluable aid to the human embryologist in distinguishing between congenital effects which can properly be ascribed to heredity and those which are more correctly regarded as due to prenatal environment and therefore likely to be more easily preventable. Professor Penrose finished his address with a plea on behalf of geneticists for more medical information, and particularly for accurate data on the frequency of congenital abnormalities in the population. Without such data pedigree studies may often be meaningless, since until we know the frequency of a condition we do not know whether its occasional presence in two relatives means anything: this will come about only with the diffusion of genetical notions in the medical profession. But had Professor Penrose been speaking to a different audience he might equally well have stressed the need for a clinical point of view among geneticists, including animal and plant geneticists. For medicine is not merely a useful art: it is a science which can and should influence all other branches of biology, including genetics.

VITAMIN-A DEPRIVATION IN MAN

Some anxiety about the adequacy of the wartime diet to maintain the health of the population was inevitable, and as a means of increasing the consumption of vitamin A in the form of carotene the Ministry of Food made strenuous efforts in advertising campaigns to popularize carrots. An insurance against severe deficiency was also provided by the compulsory addition to margarine of vitamin-A concentrates, which were mostly obtained from whale livers. Doubts still remained, however, about the exact amount of vitamin A required by human beings, and in 1942 the Medical Research Council was requested to undertake experiments to obtain definite information on this point. The report of the investigation, which was organized by the Vitamin-A Subcommittee of the Accessory Food Factors Committee, was given the title "Vitamin-A Requirements of Human Adults—A Study of Vitamin-A Deprivation in Man."[1]

The volunteers who acted as experimental subjects for these prolonged experiments were 20 young male conscientious objectors and three women. They were housed at the Sorby Research Institute, Sheffield, a large villa with some rooms converted for use as laboratories. At first the organization of the investigation was in the hands of Dr. Kenneth Mellanby, and subsequently of Professor H. A. Krebs. Most of the volunteers had already proved their reliability and patience in experiments on the transmission of scabies, and they tolerated without protest a monotonous diet made deficient in vitamin A and carotene by exclusion of foods such as butter, whole milk and its products, liver and other animal organs, fat fish, and all green and yellow vegetables and fruits. With the co-operation of laboratories at Cambridge, Liverpool, Oxford, and Reading numerous routine tests for vitamin A and carotene were carried out, both on the blood and faeces of the volunteers and on the foodstuffs which they were allowed to consume. Measurements of the capacity for dark-adaptation were made at the institute mainly by means of an apparatus designed by Mr. W. Bartley, one of the volunteers, or by rod scotometry. The scope of the investigation can be judged from the fact that the research team consisted of about 25 doctors, scientists, and senior technicians. Many commercial firms assisted by providing specially prepared foodstuffs or in other ways. The heavy task of co-ordinating the efforts of the various groups of workers was undertaken by Miss E. M. Hume.

In 16 of the volunteers who subsisted on the diet without supplements and in two who were dosed with preformed vitamin A, carotenoid pigments disappeared almost completely from the blood plasma during the first few weeks of the experiment. The decline in the plasma vitamin A, which at first ranged from 65 to about 120 i.u. per 100 ml., was less rapid, and in one subject the original level was maintained for no less than 22 months. The mean figure of 88 i.u. obtained from tests made shortly after the experiment had started fell only to 74 i.u. in nine months, and in seven subjects who remained in the experiment for 14 months the mean was still as high as 61 i.u. The decline in both plasma carotenoids and vitamin A was prevented or reduced in control subjects by daily doses of 2,500–6,700 i.u. of carotene in various forms, while the fall in the plasma vitamin A, but not in carotenoids, was prevented by doses of 2,500 i.u. of a distilled concentrate of vitamin-A esters. In the parallel dark-adaptation tests some evidence of a seasonal variation was found in all subjects, the final-rod-threshold values reflecting the variations in the monthly averages of

[1] *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 264, 1949; London: H.M.S.O.
[2] *Biochem J.*, 1937, **31**, 155.

daily minimum temperatures. Considerable deterioration in capacity for dark-adaptation not related to the season of the year was observed in only three of the volunteers who received no supplements; all three had plasma-vitamin-A values of 40 i.u. or less. Only in these cases was it possible to carry out satisfactory therapeutic tests. Preformed vitamin A, in a daily dose of 1,300 i.u. given over a prolonged period, was found both to improve the dark-adaptation and to restore the plasma vitamin A to about its original level. With a daily dose of 1,250 i.u. of carotene in oily solution the amounts of vitamin A and carotenoids in the plasma were slightly increased, but dark-adaptation was improved only when the dose was raised to 2,500 i.u. Studies of the efficiency of absorption of carotene from carrots and green vegetables were made by finding the difference between the amounts eaten and those excreted in the faeces. With allowances for a safety margin and for wastage during absorption the daily requirement of an adult male may be assessed as 2,500 i.u. of preformed vitamin A, 4,000 i.u. of carotene in oil, 7,500 i.u. of carotene in green vegetables, or 12,000 i.u. of boiled sliced carrots. With ordinary diets, of course, the daily requirement will not be derived from a single item but will be contributed by foods containing both preformed vitamin A and carotene. Larger amounts may be needed by pregnant or lactating women and by children.

Apart from the changes mentioned the volunteers had no symptoms which could be ascribed to deficiency of vitamin A, though two of them were found during the course of the experiment to be suffering from tuberculosis. While it may seem surprising that a diet containing only traces of the vitamin should have caused no symptoms of deficiency in most of the subjects, it has long been known that the human liver normally contains large reserves of vitamin A. In this country before the war Moore[2] found that the reserves present in the liver of persons who died as a result of accidents usually appeared to be sufficient to meet the body's requirements for several months, and there is nothing in the M.R.C. report to indicate that wartime dietary changes have had the effect of decreasing reserves. Nevertheless it is surprising that some of the volunteers were able to subsist on this restricted diet for 1½–2 years, and the conclusion must be that the reserves in the liver are mobilized and expended with great economy. The clear evidence of incipient vitamin-A deficiency found in three out of 16 subjects was perhaps as much as could be expected from an experiment which could not be prolonged indefinitely. Both the research team and the volunteers must be commended for their patience and perseverance in completing one of the longest and most laborious nutritional experiments yet to be undertaken in this country.

ABSORPTION OF VITAMIN B_{12}

A few weeks ago in this *Journal* Dr. Byron E. Hall[1] reviewed recent work on the intrinsic factor of Castle and described some of his own experiments which shed light on the interaction between the intrinsic factor and vitamin B_{12}. In a series of papers in this issue Dr. C. C. Ungley reports the results of carefully devised therapeutic experiments to test the absorption of vitamin B_{12} administered orally to patients with pernicious anaemia. Briefly, the investigation was concerned with the effect of normal gastric juice in promoting absorption of the vitamin, with absorption of massive doses of vitamin B_{12} alone, and with the demonstration that milk or concentrated whey does not serve as an alternative source of intrinsic factor or of protein capable of affecting vitamin B_{12} in such a way as to lead to its absorption. In addition Ungley tested the absorbability of vitamin B_{12} alone from the buccal cavity and from the intestine, absorption from the latter site being considered in relation to such possible destructive agents as the intestinal juice and bacteria.

Some investigators, using small doses or even fairly large single doses of up to 1,000 μg. of orally administered vitamin B_{12}, have obtained either no response or variable and inadequate responses in patients with pernicious anaemia,[1] though Spies and his colleagues[2] found that about 50 times the smallest parenteral dose was slowly effective when given by mouth. Goldhamer[3] has shown that the quantitatively reduced gastric juice in patients with pernicious anaemia may contain a very small amount of intrinsic factor, so that some slight absorption might be expected. Ungley has now obtained evidence that the absorption of vitamin B_{12} when administered orally in small daily doses is very poor: no response was observed in a patient given 5 μg. daily for 10 days, and in another patient receiving 80 μg. daily for 24 days a rise in erythrocytes occurred which was no greater than would be expected after a single injection of only 2.5 μg. When filtered and neutralized normal gastric juice was given with vitamin B_{12} to eight patients with pernicious anaemia the responses were variable, but indicated that each 100 ml. of juice may potentiate the absorption of from 1 to 10 μg. of the vitamin. One of these patients failed completely to respond, and another, receiving only 150 ml. of juice with 40 μg. of vitamin, responded unsatisfactorily. A remarkable result, however, was obtained in five patients receiving a single massive dose of vitamin B_{12}

[1] *British Medical Journal*, 1950, **2**, 585.
[2] *Lancet*, 1949, **2**, 454.
[3] *Amer. J. med. Sci.*, 1936, **191**, 405.
[4] *J. Amer. chem. Soc.*, 1949, **71**, 3858.
[5] Ross, G. I. M., *Nature, Lond.*, 1950, **166**, 270.
[6] Meyer, C. E., Epstein, S. H., Bethel, F. H., and Hall, B. E., *Fed. Proc.*, 1950, **9**, 205.
[7] Brink, N. G., Kuehl, Jr., Folkers, Karl, *Science*, 1950, **112**, 354.
[8] Veer, W. L. C., Edelhausen, J. H., Wijmenga, H. J., and Lens, J., *Biochim. biophys. Act, Amst.* 1950, **6** 225.
[9] Ellis, B., Petrow, V., Beaven, J. H., Holiday, E. R., and Johnson, E. A., *J. Pharmacol.*, 1950. In the press.

concentrate by mouth—3,000 μg. without added gastric juice. All responded, and, by computation from the expected response to parenteral treatment, it was considered that in no case was less than one-fortieth of the dose absorbed. Such a large dose of vitamin B_{12} is of course greatly in excess of what would normally be ingested in the diet, and it appears very unlikely that the gastric juice in these achlorhydric patients can have contained enough intrinsic factor to potentiate absorption of the vitamin in the amounts necessary to bring about such a result. The probability is, therefore, that the vitamin was directly absorbed.

Ungley's experiments on absorption of vitamin B_{12} from the intestine are of great interest, though the unavoidable difficulties render interpretation less easy. In two patients a segment of the small intestine was isolated after the passage of a Miller–Abbott tube with two balloons: the balloons were inflated and the intervening section of intestine was washed out with normal saline. Vitamin B_{12} was then instilled into the isolated segments and its absorption studied. No response occurred in either case, and microbiological tests showed that wash-fluids recovered from the segments contained the vitamin.

In both cases intubation was performed again, and this time vitamin B_{12} was instilled together with normal gastric juice. Again there was practically no response. In one case, however, the juice had been Seitz-filtered—a process which was afterwards shown to remove much intrinsic-factor activity. In the other case 500 ml. of gastric juice was given with 80 μg. of vitamin B_{12}, and the small reticulocyte response indicated only very slight absorption. This patient later responded well to parenteral therapy. There is thus no evidence for the absorption of free vitamin B_{12} from a segment of intestine protected from contact with general intestinal contents. Positive evidence for absorption of vitamin B_{12} from this site (the exact position of which is not known) in the presence of intrinsic factor is also lacking.

Perhaps a more informative experiment was that in which the bowel of a patient with pernicious anaemia was partially sterilized by oral doses of chemotherapeutic agents before he was given 80 μg. of vitamin B_{12}. No response occurred, though later, when the vitamin was given with normal gastric juice, the reticulocytes rose to 15.8% on the sixth day. Later still the injection of 80 μg. further greatly increased the rise in erythrocytes. This would seem to indicate that failure of absorption of vitamin B_{12} when unprotected by the intrinsic factor is not due to avidity of coliform organisms for it, though Hall[1] quotes an experiment by Lichtman and his colleagues with the opposite result. This problem requires further exploration, for Ternberg and Eakin[4] have observed that union of vitamin B_{12} with intrinsic factor renders it unavailable microbiologically, and Ungley and Cuthbertson have confirmed this. It is important to note, however, that, although vitamin B_{12} appears to unite with several proteins and lose microbiological activity,[5,6] Hall found the vitamin in the lysozyme complex was not absorbed when given by mouth, whereas absorption occurred when it combined with intrinsic factor in human gastric juice or swine gastric and duodenal mucosae.

The evidence to date perhaps favours the view that failure of absorption occurs in pernicious anaemia, rather than destruction of vitamin B_{12} in the intestine or its deviation to micro-organisms. In any case, union with the intrinsic factor appears to be of prime importance when vitamin B_{12} is ingested in physiological amounts, though it is of great interest that ingestion of huge amounts of the vitamin may lead—perhaps by a mass action—to by-passing of this normally essential mechanism and to direct absorption. Growing knowledge of the chemical and physical nature of the B_{12} molecule may allow the problem of its absorption to be studied in model systems. It is not yet known whether the interaction with the intrinsic factor is of the nature of an enzyme reaction, with the properties and limitations of such a system, or whether the intrinsic factor is a highly specific protein, union with which is normally necessary for active transfer of vitamin B_{12} across the barrier of the intestinal epithelium—as opposed to passive transfer of the vitamin by diffusion through what is sometimes likened to a sieve-like membrane. If the protein takes part in the absorption, it may well be a very exceptional case. But from the picture which is emerging of the vitamin B_{12} molecule, which is perhaps built up somewhat on the porphyrin model and which must be absorbed intact, its steric and other characteristics may well render its absorption a special biological problem. Also, in view of recent evidence for the fairly ready interconvertibility between vitamin B_{12} and the more chemically reactive vitamin B_{12b},[7-9] the results of complex therapeutic experiments must be interpreted with caution.

TREATMENT OF NEUROSYPHILIS

In the pre-penicillin era the treatment of neurosyphilis presented many difficult problems. Meningeal and meningovascular forms reacted reasonably well to arsenicals and bismuth, but parenchymatous forms were more resistant; and general paralysis of the insane was nearly always fatal until malaria treatment was introduced by Wagner-Jauregg. Penicillin, however, completely altered the picture, and most forms of neurosyphilis have been found to react remarkably well to it, though it is clear that even penicillin cannot restore dead nerve cells and nerve fibres. There has

been some discussion recently about whether penicillin alone can accomplish as much as penicillin combined with malaria. At a meeting of the Society for Investigative Dermatology in the U.S.A. Spiller and his colleagues[1] reported on 170 cases of neurosyphilis, 105 of which were treated with penicillin alone and 65 with penicillin combined with malaria. These patients were observed for from six months to four years or more, and the authors found that so far as the cerebrospinal fluid was concerned response was about equal with the two methods of treatment, but that clinical results were slightly better with combined treatment. Most of those who spoke at the discussion which followed this paper were in favour of using penicillin alone, and other American opinion seems to be swinging in the same direction[2 3] (as it is in other forms of syphilis). A number of workers, however, still think that fever therapy aids the action of penicillin.[4-7] In Great Britain the tendency is to assume that it is useful to have two strings to one's bow. Thus Nicol,[8] who probably has more experience of neurosyphilis, and particularly G.P.I., than anyone in this country, found that malaria plus tryparsamide gave better results than malaria alone in G.P.I., and that the best results are now obtained with penicillin and malaria. Admittedly malaria and other forms of pyrexial treatment carry a certain risk to life, but a careful technique and suitable selection of patients will reduce this to very small proportions. No doubt it is this risk, due largely to lack of experience and adequate facilities, which has led so many to give up or omit a form of treatment which has accomplished much in the past. It seems to be fairly generally agreed that in optic atrophy and perhaps active tabes dorsalis results are better with combined treatment than with penicillin alone.[9-11]

It certainly seems logical that when two forms of treatment, each of which has been shown to be effective, are available both should be employed unless there are definite contraindications. However, it may be advisable to try penicillin alone at first and if that is not successful to resort to pyrexial treatment as well. In this connexion several authors have stated that increasing the amount of penicillin beyond a certain point—4 mega units, according to Callaway and his colleagues[12]—did not improve results. The effectiveness of the treatment of neurosyphilis is judged by examination of the cerebrospinal fluid and by clinical progress, though the two do not necessarily go hand-in-hand. Admittedly it is often difficult to measure clinical improvement, but this is what the patient looks for, and the wise syphilologist will adopt that form of treatment which in his experience is most likely to restore the patient to normal or render him a useful member of the community.

[1] *J. invest. Derm.*, 1950, **14**, 121.
[2] Curtis, A. C., Kruse, W. T., and Norton, D. H., *Amer. J. Syph.*, 1949, **33**, 527.
[3] Wong, Y. T., and Packer, H., *ibid.*, 1948, **32**, 212.
[4] Kierland, R. R., O'Leary, P., and Underwood, L. J., in *Recent Advances in the Study of Venereal Diseases*, 1948, U.S. Public Health Service, 1948, Washington, p. 180.
[5] Landau, D., Kopp, I., Rose, A. S., and Soloman, H. C., *Amer. J. Syph.*, 1949, **33**, 357.
Epstein, N. N., and Key, J. M., *Arch. Derm. Syph., Chicago*, 1949, **60**, 543.
[7] Nichols, F. T., and Heyman, A., *Amer. J. Syph.*, 1949, **33**, 561.
[8] *Med. Illustr.*, 1949, **3**, 402.
[9] Benton, C. D., and Heyman, A., *Arch. Ophthal., Chicago*, 1948, **40**, 302.
[10] Packer, H., and Wong, Y. T., *Ann. intern. Med.*, 1949, **31**, 96.
[11] Fetterman, J. L., *Arch. Derm. Syph., Chicago*, 1946, **54**, 566.
[12] *Sth. med. J., Nashville*, 1950, **43**, 412.

R.S.M. SECTION OF GENERAL PRACTICE

In response to a petition promoted by two general practitioners, Drs. G. M. Kerr and G. O. Barber, the Royal Society of Medicine has formed a Section of General Practice, and its inaugural meeting will be held on November 22 at 8.15 p.m. Future meetings will be held on the third Wednesday in each month during the winter. The petition was signed by 74 specialists (Fellows of the Society) and 78 general practitioners (13 of them Fellows). This promises to be an excellent departure from tradition, and will no doubt be welcome to the many general practitioners who will be able to take advantage of it.

The objects of the Section are "to narrow the widening gap between specialists and general practitioners, to provide for the general practitioner an active link with currently accepted ideas, and to keep alive the academic or scientific attitude to medicine and its allied branches, which is so readily lost in general practice." These thoroughly desirable aims have been expressed in various ways recently, and with increasing urgency, as medicine has followed the pure sciences in developing highly specialized techniques for attacking its problems. The difficulty of keeping up to date, and of understanding the relevance to everyday clinical work of much of the research carried out in hospitals and laboratories, are sources of anxiety to general practitioners that barely afflicted their forebears fifty years ago. At the R.S.M. general practitioners will be able to hear the latest views on subjects related to their daily work expressed by the leading specialists in those subjects, and the Society provides that encouraging atmosphere where discussion can range freely over the science and practice of medicine.

There is great need for closer collaboration between these two branches of the profession than circumstances make possible at present. The sponsors of this venture and the R.S.M. are to be congratulated on starting what should be a most interesting and educative Section. It is to be hoped that similar enterprise will be shown by those medical schools and universities where the problems of general practice still receive too little attention in the curricula.

ANTI-CALCIFYING ACTION OF PHYTATE

Some thirty years ago Mellanby recognized that rickets in dogs was caused not only by the absence of a fat-soluble vitamin from their diets but also by the presence of harmful factors, which he first termed "antivitamins" and later "toxamins." A clue to the nature of these substances was subsequently given by Bruce and Callow,[1] who found that the absorption of calcium from the intestines was inhibited by phytic acid, a phosphorylated form of inositol which is present in cereals in substantial quantities. Harrison and Mellanby[2] established that phytic acid could in fact account for the rachitogenic properties of cereals when fed to dogs. Since adequate dosing with vitamin D prevented rickets even when the food contained phytate it

[1] *Biochem. J.*, 1934, **28**, 517.
[2] Ibid., 1939, **33**, 1660.
[3] *J. Physiol.*, 1949, **109**, 488.
[4] *Brit. J. Nutrit.*, 1948, **2**, 373.
[5] *J. Physiol.*, 1926, **61**, P xxiv.

seemed logical to assume that the vitamin counteracted the action of the phytate in preventing the absorption of calcium.

Further painstaking experiments by Mellanby,[3] carried out over many years, have now shown that the problem is less simple than it had seemed. Comparisons of the rachitogenic actions of phytate with those of corresponding amounts of inorganic phosphorus have given divergent results in different experiments, and the cause of the variation has been traced to irregularities in the vitamin-D reserves of the animals at the commencement of the experiment. When reserves of vitamin could be called on it was invariably found that phosphorus in the form of phytate caused more severe rickets than the same amount as inorganic phosphate, but in the absence of reserves the difference was largely obscured. Moreover, even with high doses of vitamin D phytate still reduced the amount of calcium absorbed from the intestines, with the result that bones were less well calcified and more osteoporotic than when it was absent from the diet or was replaced by inorganic phosphate. A diet high in phytate must therefore be supplemented with both calcium and vitamin D if bone formation is to be perfect. Some evidence was obtained that vitamin D may destroy phytate, and, conversely, phytate appeared to increase the rate of expenditure of the vitamin-D reserves. The main anti-calcifying action of phytate, however, presumably depends on its competition in the intestines with its structural analogue, inorganic phosphorus, for combination with calcium. According to the definition adopted by Kodicek,[4] the term antivitamin may conveniently be reserved for substances capable of interfering with the action of a vitamin by reason of their chemical resemblance to it, which allows them to compete with it in its essential reactions. Clearly the action of phytate is not covered by this definition, and its description by Mellanby[5] as a "toxamin" is therefore perhaps more appropriate.

INHALATION DURING DENTAL EXTRACTION

In a study of 316 non-malignant lung abscesses Brock[1] found that 7% occurred after the removal of teeth. He suggested four main causes for this sequel: multiple extractions under deep anaesthesia; the extraction of septic teeth with tartar masses; the upright position of the patient in a dental chair; and inexpert anaesthesia. Fry and Earl[2] have now published a preliminary report of their attempts to assess the importance of each of these factors in encouraging the inhalation of blood and other debris during dental extraction. They investigated two small series of patients by injecting 2–3 ml. of radio-opaque oil into the buccal sulcus before or during the extractions and radiographing the chest within 30 minutes of the patients' return to consciousness. In their first series of 24 unselected patients undergoing extractions under nitrous-oxide anaesthesia none inhaled a demonstrable quantity of oil. The second group was of 14 patients subjected to multiple extractions, two of whom were anaesthetized with trichlorethylene and the remainder with nitrous oxide. The oil was injected midway through the operation, when the throat-pack was soaked in blood. Only one patient—a man who had seven teeth extracted—was found to have inhaled the oil, which was seen in the right lower-lobe bronchus. The number of patients studied by Fry and Earl is too small to allow firm conclusions to be drawn. The radio-opaque oil used was not miscible with blood and was usually about one-tenth of the volume of blood in the mouth. That no oil was inhaled is therefore no indication that blood was not. This work has, however, demonstrated that inhalation can occur during dental extraction without the knowledge of the operator, and it justifies similar investigations on a larger number of patients, preferably with a radio-opaque substance that mixes freely with blood.

[1] *Guy's Hosp. Rep.*, 1947, **96**, 141.
[2] Ibid., 1950, **99**, 41.

CARDIAC DISEASE AND PREGNANCY

Two recent papers have added to the voluminous literature about cardiac disease and pregnancy. Vander Veer and Kuo[1] studied the records of 409 pregnant women with heart disease—324 with rheumatic, 51 with hypertensive, 18 with congenital heart disease, and 16 with miscellaneous cardiac abnormalities. The mortality was 3.4%, and death was due to congestive failure, apart from one case of ruptured aorta (coarctation), two of bacterial endocarditis, and one of acute exacerbation of rheumatic endocarditis, though this presumably also caused death through cardiac failure. According to some British cardiologists acute rheumatic carditis is an important cause of breakdown in pregnancy, and it may be that this infection is more frequently responsible for failure than is suspected. Pneumonia occurred in four of the patients, though it might be questioned whether this was the cause or the result of the failure. In seven of the ten fatal cases in which congestive failure occurred death took place between the seventh and eighth months of pregnancy. The other three patients died from pulmonary oedema within two days of delivery. The authors state that the reason for this post-partum failure is obscure; certainly their suggestion that it may be caused by blood loss is not acceptable, since venesection gives relief in acute pulmonary oedema. They do not advise abdominal delivery, except perhaps for patients with hypertensive disease. Their recommendations for preventing heart failure are based on well-known principles, according to the severity of the case: first, pregnancy may have to be avoided; secondly, it may have to be terminated in the early months; and, thirdly, close watch must be kept for the earliest signs of failure or other complications. That several pregnancies in women with rheumatic heart disease are quite compatible with the attainment of middle age has been shown by Correll and Rosenbaum,[2] who looked into the records of 53 women who each had from four to sixteen pregnancies. Fifty-two had rheumatic and one congenital heart disease. Out of this total 34 patients had died, the average age at death being 49.5 years. It is quite possible that a number of pregnancies may not occasion any symptoms in a woman with heart disease, and in fact the disease may not be discovered until her children are grown up. It is very different, however, where symptoms have already made their appearance, and in such cases it must be remembered that pregnancy, labour, and, not least, the upbringing of children are additional burdens.

[1] *Amer. Heart J.*, 1950, **39**, 2.
[2] Ibid., 1950, **39**, 283.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE TREATMENT OF ULCERATIVE COLITIS

BY

G. E. BEAUMONT, D.M., F.R.C.P.

Physician, Middlesex Hospital

One of the most eminent teachers of clinical medicine at the Middlesex Hospital is reputed to have said to his students, "The most important thing you have to learn while in the wards is to diagnose the nature of a patient's illness. Once the diagnosis is made the treatment can be looked up in a book."

Like so many epigrammatic statements this is only a half-truth. One of the differences between a newly qualified practitioner and an experienced doctor is that the latter has himself tried various treatments for various diseases, and has found out which are the most successful. There is no doubt that the best way of learning therapeutics is by treating a series of cases oneself; the second best way, perhaps, is by reading detailed accounts of cases treated by others. And so readers of the Refresher Course who still continue to treat at home, or in nursing-homes, the patients who are seriously ill, and do not send them all into hospital, may be interested to read about one or two patients suffering from ulcerative colitis whom I have treated, and to see how they have fared.

One afternoon, when I was teaching on such a case in my ward, I asked a postgraduate student what treatment he would advise. He replied, "Forty treatments have been recommended, but none of them are any good." When I suggested that he might unmuzzle his wisdom he reeled off the following list: vaccines, sera, special diets, sulphonamides, penicillin, bacteriophage, pneumoperitoneum, psychotherapy, vitamins, blood transfusion, oxygen per rectum, astringents and antiseptics per rectum, and various operations such as ileostomy and high colostomy, appendicostomy and caecostomy, and colectomy or hemicolectomy.

Recognizing that he had read a recent article on ulcerative colitis in a medical journal, and not wishing to be outdone, I added to the list ileal extracts taken by mouth, protein hydrolysates, ionization, artificial-fever therapy, and vagotomy.

If we are to adopt this nihilistic view about the treatment of ulcerative colitis I may as well close my article now; but I am not so pessimistic, though I know that in this disease relapses are apt to occur after apparent cure. I propose to give some details about two cases that I treated.

Illustrative Case 1

A married woman aged 31 was admitted to hospital on July 29, 1946. She looked very ill, was pale and thin, and had lost over 2 st. (12.7 kg.) in weight during the last 15 months, weighing now only just over 6 st. (38.1 kg.). She lived in a damp cottage in the country with a concrete floor; there were four children at home under the age of 9 years; and her husband, who worked as a nursery gardener, had a partially paralysed left arm resulting from war wounds. The house-physician described her as being "of a worrying type and rather introverted." In addition to household cares the patient was concerned about the reduction of her husband's war pension. It was difficult to get an accurate history of the illness, but it appeared that blood was first noticed in the stools in August, 1944, during pregnancy. The bleeding was attributed to piles, though at this time the patient also suffered from abdominal pain and diarrhoea. After parturition the diarrhoea stopped. In September, 1945, there was a recurrence of diarrhoea with blood in the motions, and severe griping abdominal pains, which the patient described as "worse than having a baby." This continued until admission to hospital.

Further examination showed that the mucous membranes were very pale, the teeth carious, and the blood pressure low—100/70 mm. Hg. Her temperature was raised to about 102° F. (38.9° C.) in the evening, falling to 99 or 100° F. (37.2 or 37.8° C.) in the morning. The abdomen was distended owing to flatulence; the transverse and descending colon was palpable and very tender. The urine was normal. The bowels were opened on an average six times by day and six times by night.

The first steps in the treatment of such a case were to exclude other causes of diarrhoea, to determine the degree of anaemia, and to establish the diagnosis of ulcerative colitis. The agglutination tests on the blood serum were negative for the typhoid and paratyphoid, and the dysentery and para-dysentery groups of organisms. The stools showed no amoebae or cysts, no ova, and no pathogenic organisms. There were numerous degenerate pus cells, red corpuscles, and macrophages. On culture only *Bact. coli* types of organisms were grown. The blood count indicated a severe hypochromic anaemia, with haemoglobin 55%, red corpuscles 2,000,000 per c.mm., colour index 0.65, white cells 6,600 per c.mm. (polymorphs 53%, lymphyocytes 43%, monocytes 4%). The corrected sedimentation rate of the red cells was 13 mm. % plasma at one hour. Sigmoidoscopic examination showed numerous bleeding ulcers about 5 in. (12.7 cm.) from the anus, with mucosal polypus formation.

Looking back on the cases of ulcerative colitis which I have treated during the last 30 years, I think that the greatest advance has been in the use of blood transfusions in severely anaemic patients. It is impossible to raise the blood count to normal by giving iron by mouth when the blood is steadily dripping away below. Further, the blood transfusions help to restore the plasma albumin, which is always likely to be low, and also aid in effecting an adequate mineral concentration in the blood.

In this case we found the plasma albumin to be 2.3 g. % instead of the normal 4.5 to 5.2 g.%. The figures for the plasma globulin and fibrinogen were normal. The patient was first given ½ gr. (32 mg.) of phenobarbitone three times a day to calm her generally, and 1/200 gr. (0.32 mg.) of atropine sulphate in water by mouth three times a day to cut down vagal and sacro-pelvic parasympathetic nervous impulses to the colon. Bismuth and kaolin preparations must not be given, as they may cause caking of the intestinal contents and pressure necrosis of the intestine. When the abdominal pain was very severe in the early stages, relief was obtained from 15 min. (0.9 ml.) of tincture of opium in water. The patient's blood was found to belong to Group O, and 3 pints (1.7 litres) of compatible blood was given by drip transfusion intravenously.

Ten days or so later, on August 23, the patient said that she was feeling much better; the diarrhoea had almost ceased, the bowels now being opened on an average three

times in the 24 hours. The temperature, however, was still raised to 100 or 101° F. (37.8 or 38.3° C.) in the evenings. In addition to this treatment, a high-protein, high-calorie, and low-residue diet was ordered, the septic teeth were removed under a penicillin "screen," and sulphaguanidine, 1 g. every six hours, was given by mouth for two weeks. Vitamin B complex was administered, two capsules daily, and 4 ml. of "hepastab" was injected intramuscularly every four days. The diet was of necessity subject to war-time restrictions, but a more varied one, which can be obtained now, is given below.

The haemoglobin rose to 66% on August 26 and remained at this level for another four weeks. By the end of September there was no diarrhoea, no blood in the motions, no abdominal pain, but also no gain in weight.

Relapses

During October there was a relapse. The temperature, which had been normal for a week, rose again, with recurrence of diarrhoea, the bowels being opened five times in the 24 hours and the motions containing blood. On October 18 a further blood transfusion was given of 2 pints (1.1 litres), with good results. The temperature fell to normal, the diarrhoea ceased, and the haemoglobin rose to 77%. In a week or so the patient was able to walk around the ward, and she returned home at the end of November. She was now feeling well, had a good appetite, was satisfied with her treatment, and was gaining weight at the rate of 3½ lb. (1.6 kg.) a week.

But this happy state of affairs did not, unfortunately, last long. Two weeks after returning home she relapsed, and her doctor wrote, "The circumstances of her home are absolutely shocking and her idea of diet hopeless." I recommended her to come into hospital again, but she was unwilling to do so, saying that she must look after her home. She remained partly in bed at home, and by the end of March, 1947, was much better. She was very fit during the summer, being able to walk four to five miles (6.4 to 8 km.) a day, and her weight increased to 10 st. 9 lb. (4.8 kg.). One day in September, while carrying a pail of water from the well in her garden to her house, the diarrhoea recurred, with the passage of blood in the motions. The patient, however, kept on with her household work until December 24, 1947, when suddenly there occurred a shivering attack, high temperature, severe abdominal pain aggravated by any movement, diarrhoea, and at times incontinence of faeces. Various opium preparations were administered, but she continued to lose weight, and finally was again admitted under my care in hospital on March 9, 1948.

When I saw the patient I could tell at once that, although very pale, she was not nearly so ill as on the first admission. Her temperature was normal; her weight, however, was very low—6 st. 8 lb. (2.9 kg.). She said she could feel "hard lumps" running across the abdomen from right to left, which resolved themselves into the passage of mucus and wind. The motions were loose, containing mucus but no blood, and the bowels were opened about once by day and six times by night.

This preponderance of night motions is interesting, and is probably due to an exaggeration of the normal predominant activity of the parasympathetic over the sympathetic during sleep. The haemoglobin was lower than it had been before, 32%, and the red cells numbered 3,200,000 per c.mm. A drip transfusion of 3 pints (1.7 litres) of blood was given on March 14, the haemoglobin rising to 60% and the red cells to 3,900,000 by March 18. During the next two weeks the diarrhoea ceased and there was a gain of 8 lb. (3.6 kg.) in weight. In addition to the transfusion, phthalylsulphathiazole was given by mouth in doses of 1 g. three times a day for two weeks, and "trasentin" tablets, 75 mg., one or two a day, as required for abdominal pain. A mixture containing 30 gr. (2 g.) of ferric ammonium citrate was taken three times a day, and 200 mg. of ascorbic acid daily.

On April 3 the patient returned home again, feeling and looking very much better. I had not heard any more about her, and so, before completing this article, I wrote to her doctor, and he replied, "She does not suffer from diarrhoea so much, but has tenesmus and is continually passing some mucus and blood. She says she is too ill to go outside. The anaemia is not so obvious, but the tongue is very pale. Though the legs are not swollen the abdomen has enlarged considerably. I cannot feel anything. Her periods occur every three weeks." I suggested the advisability of another blood transfusion and protein hydrolysate, two teaspoonfuls three times a day with meals.

Diet

The following diet contains approximately 385 g. of carbohydrate, 145 g. of protein, 115 g. of fat: 3,155 calories.

Breakfast.—Milk 8 oz. (230 ml.), porridge (strained) 1 oz. (28 ml.), crustless bread 3 oz. (90 g.), sugar ¼ oz. (8 g.), 1 egg, and bacon 1 oz. (30 g.), or fish 4 oz. (120 g.), butter ¼ oz., pipless jam or honey or syrup ¼ oz.

Lunch.—Cream soup (canned) 10 oz. (280 ml.), meat (minced) 2 oz. (60 g.) or fish 4 oz. or cheese 2 oz., mashed potatoes 6 oz. (180 g.), purée of vegetables 4 oz. (120 g.), pudding made from milk 8 oz., semolina or other cereal ½ oz., fruit purée as desired, sugar ¼ oz.

Tea.—Milk 2 oz., crustless bread 2 oz., butter ¼ oz., sponge cake or plain cake without fruit 2 oz., pipless jam or honey or syrup ¼ oz.

Supper.—As for lunch.

On Waking, at 11 a.m., and Last Thing at Night.—Milk 2 oz., cocoa ¼ oz.

The cream soups may be thickened with dry potato powder. Syrup may be used as desired in sweets. The sweet ration should be taken as chocolate. Yoghurt and fruit juices, such as blackcurrant juice and rosehip syrup, make a useful change from the usual pudding. Very ripe bananas, if available, may be taken, as may be sweetbreads, brains, or kidneys.

Some doctors prefer that their patients should not be ordered a low-residue diet, and consider that a certain amount of roughage is beneficial. I do not agree with this. I think it is of importance to avoid raw fruit. I have known an orange, or one or two grapes, brought in by visitors, cause a relapse in a patient who was doing well.

Illustrative Case 2

In December, 1947, I was asked to see a married man aged 45, suffering from the same complaint, in whom the nervous or psychological symptoms were more in evidence. The doctor told me that the patient had suffered from digestive trouble all his married life, chiefly nervous symptoms, nausea, fainting, and appendix pains. He belonged to a more educated class than the first patient, being employed in one of the Ministries, and he was afraid that he would not "make the grade" for establishment. In addition to the anxiety thus produced, he was worried about financial commitments on a house into which he had just moved.

We are all familiar with the literature during recent years dealing with the psychiatric aspects of ulcerative colitis, and

the emphasis placed by some writers on what is termed the "grief response." Stress has also been laid on the dependent personality of many victims of this disease and the close physician–patient relationship which develops during treatment. The cause of ulcerative colitis is not known. It is described as a psychosomatic illness, which means, I believe, that a disorder of the mind produces a disease of the body, and as Sir Toby Belch said, "I am sure care's an enemy to life." The treatment recommended by some seems rather unfair—to cut out the innermost portion of the body which is the victim of the disorder of the mind, rather than to cure the diseased mind by psychological treatment. The latter, however, is found to be of little value. I have not been able to discover convincing evidence in my cases to support the view that a disturbed mind produces a diseased colon, rather than vice versa, and one of my patients told me recently that the diarrhoea resulted in "frayed nerves."

The patient said that he considered another factor in the production of his illness was overwork, both during and after the war. During 1944 he suffered from mild diarrhoea for four weeks, followed by an attack lasting for six weeks in 1945. In 1946 there was a severe attack of lichen planus, perhaps due to nervous disturbances.

When I was consulted on December 7, 1947, the diarrhoea had already lasted for five weeks, accompanied by the passage of blood and mucus. The patient suffered from colicky abdominal pain, intermittent fever, loss of weight, and was confined to bed. His own doctor had prescribed a course of sulphaguanidine followed by phthalylsulphathiazole, without beneficial results, and ten days before my visit had called in a surgeon, who advised a permanent transverse colostomy, saying that medical treatment would be of no avail. A barium enema examination had shown absence of the normal haustrations in the transverse and descending colon. The haemoglobin had fallen to 77% on November 27; the faeces contained much pus and yielded a growth of Morgan No. 1 bacillus.

Question of Operative Treatment

I was asked my opinion: should the patient submit to this operation with its unpleasant aftermath, or could I suggest an alternative form of treatment?

I should like to say a few words here about the operative treatment of ulcerative colitis. We are all agreed that if an operation is to be performed it should not be delayed until the patient is so debilitated that the chance of recovery is slight. The object of any operation is to give complete rest to the affected colon, and this can be most efficiently done by ileostomy, unless a colostomy can be performed in a healthy area of the colon. The ileostomy will have to be permanent in most cases, but a special bag can be worn—the Koenig–Rutzen bag—which is illustrated in the paper by Hardy and his colleagues (1949). McKittrick and Moore (1949), in America, record their experience of 149 cases of ileostomy, with a mortality rate of 22% and about 70% of the patients expressed themselves subsequently as well satisfied with the operation. In others the operation was a failure: one patient committed suicide; another wrote, "the whole thing is a mess, whatever I do." Is a permanent ileostomy too high a price to pay for health?—that is the question.

My answer in this case can be guessed with little difficulty. The patient came into hospital on December 13. The bowels were now opened three to four times during the day and four times during the night. The motions contained mucus and blood, but no abnormal organisms were found on culture. There was a moderate degree of anaemia, the blood count showing: haemoglobin, 79%; red cells, 4,300,000 per c.mm.; C.I., 0.9; white cells, 12,900 per c.mm., with a normal differential count. The corrected sedimentation rate of the red cells was 18 mm. % plasma at one hour. The temperature was normal. This did not appear to be a very severe case of ulcerative colitis, and the psychological factor was a much more prominent feature than in the case previously described. The patient was given a course of phthalylsulphathiazole, 1 g. three times a day for 14 days together with a high-calorie, high-protein diet, 200 mg. of ascorbic acid daily, and 6 gr. (0.4 g.) tab. ferrous sulphate thrice daily.

By December 26 the motions were reduced to four in the twenty-four hours, and they were more formed. Three days later no blood was seen in the motions. On January 1, 1948, the bowels were opened once by day and once by night and the motions were formed. A week later the patient said he felt very well and was pleased with his progress and hopeful of recovery. On January 15 the bowels were opened only once in the twenty-four hours, and sigmoidoscopy showed a healing mucosa, with some residual infection. There was excess of mucus in the bowel lumen, but no blood. The patient soon returned home, having gained 2 lb. (0.9 kg.) in weight.

On March 1, 1948, a further examination was made at hospital. There had been a gain of 18 lb. (8.2 kg.) in weight in the past six weeks and the patient had been working for two weeks. He was completely free from intestinal symptoms, but was still anxious about his work, though every effort had been made to encourage self-confidence.

In this case the degree of anaemia and the condition of the patient did not indicate the necessity for a blood transfusion.

In 1950 I wrote to the patient's doctor inquiring about further progress, but he told me that the patient had now left him. I then wrote to the patient, and he replied that he was very well.

Conclusion

The cause of ulcerative colitis being unknown, treatment must be symptomatic, and repeated blood transfusions are of the greatest value. The ultimate results, however, are very unsatisfactory. In the series of Hardy *et al.* (1949) ileostomy was performed on 21 patients, with six deaths, but half of these deaths were said to be avoidable. Of the last nine patients operated on, however, only one died.

Comanduras, in America, wrote that the word "cure" must not be used; "arrested stage" is preferable, and two-thirds of those who have been operated on will be dead after a few years. Rice-Oxley and Truelove (1950) investigated the records of 72 new cases treated at the Radcliffe Infirmary, Oxford, from 1938 to 1948; of these, 22 died within a year of onset, and one-third of the remainder had succumbed at the end of five years. Recurrences were frequent, and emergency ileostomies did not seem to be justified.

References

Hardy, T. L., Brooke, B. N., and Hawkins, C. F. (1949). *Lancet*, **2**, 5.
McKittrick, L. S., and Moore, F. D. (1949). *J. Amer. med. Ass.*, **139**, 201.
Rice-Oxley, J. M., and Truelove, S. (1950). *Lancet*, **1**, 663.

A special advisory committee has been formed by the American Heart Association in order to develop public-health work in the field of cardiovascular diseases. The committee will provide detailed practical plans which can be carried out by local heart associations for the benefit of cardiac patients in their areas. The chairman of the committee is Dr. William A. Brumfield, jun., deputy commissioner of the New York State Department of Health.

CONGRESS OF INTERNAL MEDICINE, PARIS, SEPTEMBER, 1950

The First International Congress of Internal Medicine, held in Paris from September 11 to 14, proved a success. Over 1,000 delegates attended, representing some 46 different countries. The president of the Congress was Professor A. Lemierre, and the secretary, on whom fell a very heavy burden of duty, Professor L. Justin-Besançon.

In his presidential address Professor Lemierre (Paris) made a strong plea for the continuance of general specialists in internal medicine to counteract the growing tendency to divide into narrower specialties, and indeed this theme might be said to have been echoed by the very wide range of subjects included in the Congress programme. Inevitably this meant that often two or more Sections had to meet simultaneously, so that those visitors attempting to take the broader view were sometimes unable to hear all the papers they had earmarked. Nor did all the speakers attend to deliver their addresses, and several star attractions of the published programmes were missing on the day. The majority of the papers were, however, published either in full or in abstract before the Congress in the *British Medical Journal* (September 9), *Acta Medica Scandinavica* (Special Supplement), *Schweizerische Medizinische Wochenschrift* (September 9), and *La Semaine des Hôpitaux de Paris* (issues of August 30 to September 10).

Antibiotics

Tréfouël (Paris) opened with a review of the development of the sulphonamides and sulphones from the first "prontosil" to the recent work on the synergism between the sulphones and streptomycin in tuberculosis, the use of sulphones to delay the onset of streptomycin-resistance, and to their value in treating leprosy. The next paper was by Waksman (U.S.A.), who reviewed the development of streptomycin and discussed the possible future value of "neomycin" in dealing with streptomycin-resistant organisms. Bernard, Kreis, and Lotte (Paris) followed with an account of their experiences with streptomycin therapy: 47% of their cases of miliary tuberculosis died, usually owing to meningitis. In the surgical treatment of tuberculosis streptomycin should usually be reserved for possible post-operative complications, such as miliary spread or bronchopneumonia. Lehr (U.S.A.) reviewed the principles of mixed sulphonamide therapy and its value in preventing crystalluria, and Dugger (U.S.A.) contributed a review of "aureomycin."

In subsequent discussion Dubois-Manne (Brussels) analysed 103 cases of proved tuberculous meningitis: 31% of these survived more than a year after cessation of therapy. Todorovitch (Belgrade) surveyed 851 cases with a similar recovery rate (32%). The treatment of 38 cases of renal tuberculosis with streptomycin was discussed by van Goidsenhoven (Louvain): in unilateral cases nephrectomy may be aided by a streptomycin umbrella, and early inoperable cases be much improved by a long course. Like Bernard (Paris) he had found vestibular commoner than cochlear reactions with streptomycin and the reverse with dihydrostreptomycin. Tapie (Toulouse) described a single case of tuberculous meningitis in which relapse occurred three times after premature cessation of treatment. Vidal and Plane (Montpellier) reviewed the place of streptomycin therapy in chronic pulmonary tuberculosis. It should be regarded as an adjunct to collapse therapy rather than as a rival. It may promote contracture of cavities. It is not indicated for early or isolated lesions. Janbon and Bertrand (Montpellier) gave their experience of the use of aureomycin in 80 varied cases of brucellosis: 45 were followed up for over six months after treatment, which usually lasted 30 days, and of these 30 definite cures were obtained. Results are considered better than with streptomycin or vaccine therapy. Monasterio, Gigli, and Sica (Pisa) reported on similar studies.

Radioactive Isotopes

This Section was opened by Pochin (London), who presided and gave an opening survey of the ways in which radioactive isotopes may be used to study dynamic biochemistry in health and disease, using his own work on iodine in thyroid disease to illustrate his survey. Hevesy (Stockholm) reviewed briefly the results of many other workers with isotopes. Heavy nitrogen had been used to measure the life of the erythrocyte, and radiophosphorus incorporated in desoxyribonucleic acid had shown that many lymphocytes with an unusually long life circulate in the blood in chronic lymphatic leukaemia.

Fauvert and Loverdo (Paris) described in detail their work with radiosodium in normal and abnormal conditions, showing how it measures the sodium space and how it reveals the extraordinarily high rate of interchange between the plasma and extracellular fluid. Sodium space is much increased in ascites and oedema, but thiocyanate space estimations may not reveal it. Nylin (Stockholm) recorded his use of radiophosphorus-labelled erythrocytes to determine the rate of mixing with the recipient's blood after intravenous injection. By this means it was possible to demonstrate the slowing of the circulation in shock despite a normal blood volume, perhaps to detect intracardiac shunt, and to follow progressive changes in blood volume. The legs were found to contain 20% of the circulating blood, and each lung might contain as much as 20%. Querido (Leiden) showed that observation of the effects of thyrotropic hormone, by following uptake of radio-iodine, may give better information than B.M.R. or creatine output in analysing the causes of thyroid deficiency.

Endocrinology

This Section was opened by Carlisle (U.S.A.) with a general review of cortisone, its nature and uses (see *Journal*, September 9, p. 590). Luft and Sjögren (Stockholm) found that D.C.A. (deoxycortone acetate) and salt raised normal blood pressure. A greater rise occurred in chronic renal disease with normal blood pressure. D.C.A. tablet implants had been successfully used in treating symptoms due to orthostatic hypotension. Ohlagen (Stockholm) reported that both cortisone and A.C.T.H. rapidly restore the electrophoretic pattern of the plasma proteins towards normal, especially in rheumatoid arthritis. Globulin changes are the first to regress after the cessation of therapy. Lederer and Deves (Louvain) described three cases of adrenal virilism which developed hyperthyroidism, and one case of myxoedema which developed adrenal virilism. They believe adrenal disorders are not uncommon in hyperthyroidism. The nature of the excreted 17-ketosteroids is often abnormal. Azerad and Cloche (Paris) described the electroencephalographic changes in Addison's disease. Normal alpha waves may be completely absent. (Thorn in U.S.A. finds these changes a useful criterion of adequate treatment.) Raab (U.S.A.) gave a critical analysis of the interrelations between the sympathetic system and sodium retention in producing the hypertension due to D.C.A.

Coello and da Costa (Lisbon) described two typical cases of Cushing's syndrome. One died with nephrosclerosis and at necropsy the pituitary gland was found quite normal without any Crooke hyaline changes. Only slight changes were found in one adrenal. The second case was improved by unilateral adrenalectomy. Bastenie, Gepts, and Tagnon (Brussels) reviewed 14 cases of myxoedema of pituitary origin. They proposed as a useful test of a pituitary origin in these cases the failure to obtain a drop in eosinophils after insulin hypoglycaemia, and recalled that if there is adrenal insufficiency treatment of such cases with thyroid may precipitate Addisonian symptoms. Justin-Besançon and Klotz (Paris) described detailed studies of a myxoedematous dwarf of 18 years; the condition was due to chromophobe adenoma of the pituitary, which was removed. Coste and Delbarre (Paris) reported their clinical and experimental results with the use of a preparation of A.C.T.H. largely made by themselves. With Georges, Bourel, Basste, and Lacronique they confirmed much of the work of Sayers and of Thorn in America. In contrast to the latter they found the eosinophil drop after adrenaline an unreliable test for Addison's disease. Adequacy of A.C.T.H. treatment could be controlled by the eosinophil drop. Clinical remissions in rheumatoid arthritis were obtained, but in one the response was poor with A.C.T.H. but considerably better with cortisone. Successes in

severe allergy, in asthma, and in acute gout were obtained, but the response in disseminated lupus erythematosus was disappointing. Mach and Ducommun (Geneva) had found that in rats A.C.T.H. prevents the peritoneal adhesions normally caused by talc; once formed, however, A.C.T.H. does not remove them. Justin-Besançon and Klotz (Paris) produced a penetrating review of spasmophilia in adults and older children. The weakness of many tests for latent tetany was pointed out and a plea was made for further research on the C.S.F. in such cases.

Liver and Spleen

Ascoli (Palermo) opened this Section with a review of the value of stimulating the spleen to contract, by daily intravenous adrenaline, in the treatment of many chronic infections associated with splenomegaly such as malaria and undulant fever. Askupmark (Uppsala) followed with a review of the functions of the spleen, and classified the causes of splenomegaly and also the indications for splenectomy. Frugoni (Rome) presented a full analysis of the present status of Banti's syndrome, discussing its relationship to splenic anaemia, splenic thrombophlebitis, and other conditions. Hittmair (Innsbruck) reviewed nine cases of hypersplenism: splenectomy is indicated if increasing marrow damage is evident, and when in spleen puncture signs of myelopoiesis are found. Odin (Gothenburg) reviewed the incidence of inoculation hepatitis in that city. It was high in diabetics. Sterilization of instruments by ether or alcohol is inadequate for prevention. Cachera, Lamotte, and Lamotte-Barrillon (Paris) had studied 82 chronic alcoholics by repeated liver biopsies: 87% showed a steatosis which was often massive. The fatty accumulation was not due to degeneration. The course was very variable, and even a massive steatosis might disappear. The development of cirrhosis in such livers was followed. Farah (Alexandria) introduced an unusual and provocative note by claiming that jaundice is a natural defensive mechanism in certain infections. He found that animals whose muzzles are normally near the ground have no bilirubin in the blood, whereas those with noses higher in the air have bilirubin. The latter are naturally more exposed to airborne organisms, which are generally bile-soluble. Alessandri and his colleagues (Santiago) reported on the results of 52 splenectomies in different conditions. Cure was usual in familial haemolytic jaundice but unusual in the acquired variety. Pedro-Pons (Barcelona) gave a review of splenomegalic cirrhosis. He concluded, as had Frugoni, that true Banti's disease is seldom encountered. Ducci (Santiago) reported on flocculation tests in jaundice. Gamma globulin added to normal serum gives a positive reaction, which does not occur when it is added to post-hepatitis serum. Sherlock (London) presented studies on 14 cases of obstructive-type jaundice in none of which could be demonstrated extrahepatic obstruction. She believed that obstruction occurs nearer the bile canaliculi in such cases. Kleeberg (Jerusalem) made a plea for the wider use of the Weltman reaction in medicine. He considers it more useful than the sedimentation rate. Lacroix, Antoine, and Plane (Algiers) had used Ascoli's adrenaline therapy in Algerian splenomegaly. Marked diminution in splenic size was achieved. Cachin and Martinet (Paris), reviewing the fibrocongestive splenomegalies, concluded that Banti's disease includes a variety of splenomegalies of different type and aetiology, in many of which the cause is unknown. Janbon (Montpellier) had studied the jaundice complicating streptomycin therapy. Lebon and Eisenbeth (Algiers) reviewed primary carcinoma of the liver: they preferred to distinguish three clinical types—an acute, a post-cirrhotic, and a type presenting as a tumour mass; pathological classification they found of doubtful clinical value.

Renal Diseases

Diaz (Madrid) presented a review of the lipoid nephroses. Vallery-Radot and his colleagues (Paris) gave an exhaustive review of post-abortion anuria, its pathogenesis and treatment. They agreed with the British school that in the anuric phase peritoneal dialysis, the artificial kidney, etc., are unsatisfactory, and that the main dangers arise in the polyuric phase when glomerular function is restored. Careful control of the water and electrolyte intake is then of great importance. Salvesen (Oslo) made a plea for the wider use of alkalis in treating the acidosis of chronic nephritis; in amyloid disease, polycystic kidney, and renal rickets it may also be valuable. Care is needed to avoid alkalosis or tetany. Brulls, Divry, and Louis-Bar (Liége), using their own perfusion technique on animals, concluded that the level of blood flow through the kidneys is of much greater importance than anoxaemia in causing oliguria in cardiacs or the Goldblatt phenomenon. Derot, Bernier, Legrain, and Pignard (Paris) described the treatment of 50 cases of acute nephritis with anuria: if blood urea rises above 400 mg. they resort to exsanguino-transfusion or peritoneal dialysis. Cardiac function must be watched during recovery. Testosterone appears to be of value in reducing nitrogen breakdown. Langeron and his colleagues (Lille) described the value of sodium thiosulphate as a measure of glomerular filtration-rate in the clinical study of renal function. Poli (Milan) had studied changes in plasma-protein synthesis in nephrosis, and Malendro (Spain) described two cases of chronic hepatonephritis—one probably due to syphilis, the cause of the other being unknown. Iversen and Brun (Copenhagen) reported their work on aspiration biopsy of the kidney, correlating the histology with function studies. Langeron and his associates (Lille) described a new drug, theophylline-thanoate of diethylenediamine. It has a diuretic and anti-asthmatic action, appears to improve the coronary circulation, and improves renal elimination of both chloride and urea.

Pulmonary Diseases

Bjorkman and Carlens (Stockholm) reviewed the results of their lung-function studies in which they used a new type of double-lumen bronchial catheter so as to allow the study of each lung separately. Heimbeck (Oslo), from 20 years' study of 9,000 cases of pulmonary tuberculosis, discussed the relation of morbidity to severity and duration of infection. Kourilsky (Paris) reviewed in detail the bronchial suppurations. Castex and Capdehourat (Buenos Aires) described the medical treatment of hydatid cysts (see *British Medical Journal*, September 9, p. 604). Paraf had treated tuberculosis with "P.A.S.," and Tapie and his team (Toulouse) reported a case of Hodgkin's disease of slow progression, passing through three pregnancies and complicated by bronchial compression. Brocard and Brincourt (Paris) discussed the special problems of the pathogenesis and treatment of early bilateral pulmonary tuberculosis.

Cardiovascular Diseases

Lian and Welti (Paris) presented their results in making femoral arteriovenous anastomoses in the treatment of obliterative arteritis and of severe hypertension; improvement resulted in several cases. Donzelot, Durand, and Matiani (Paris) discussed the clinical diagnosis of congenital heart disease in the light of their own series of 740 cases. Condorelli (Italy) discussed the pulmonary-artery circulation and Chavez (Mexico) new diagnostic methods. Plotz (New York) discussed the relationship between fat metabolism and coronary atheroma. Gotzche and Warburg (Copenhagen) presented the results of their studies of intracardiac pressures in 400 cases submitted to cardiac catheterization. Gilbert-Queralto (Barcelona) presented his pioneer work on left intracardiac electrocardiography and showed the types of curve obtained. No serious accident had followed catheterization of the brachial artery for this purpose. Kerr (San Francisco) stressed the value of abdominal binders in relieving the emphysematous who are also obese. Bay (Buenos Aires) recommended the subcutaneous injection of 5% carbon dioxide in oxygen for advanced intermittent claudication with gangrene. Nyman (Stockholm) described a new sympatholytic agent of dibenamine type which has rapid, intense, and prolonged action. It is beta-chloro-ethyl-ethyl-ammonium bromide. Sakellaridis and Darmar (Istanbul) analysed the effects of ventricular aneurysm on the E.C.G.: a persistent ST elevation occurs in precordial leads. Dubost and his colleagues (Paris) had grafted a preserved human aorta in a case of aortic isthmus stenosis.

Tropical Diseases

Shortt (London) reviewed recent knowledge of malarial parasites with special reference to the exo-erythrocytic cycle. The treatment of amoebiasis with "chloroquine" and with aureomycin was discussed by Conan (Beirut) and Bossa (Naples) respectively.

Haematology

In this section Hall (U.S.A.) reported his work on the intrinsic factor of Castle (see *British Medical Journal*, September 9, p. 585). Bornsdorff (Helsinki) had found that pernicious-anaemia patients fell into two groups, those that reacted to oral B_{12} without the addition of gastric juice and those that did not react even with gastric juice. Kristensen (Stockholm), by attaching a pendulum to clotting blood, could more readily measure the rate of coagulation. Gullberg (Stockholm) recommended urethane as an adjunct rather than a substitute for *x*-ray therapy in leukaemia. Urethane may produce a longer remission in myeloma. Bernard (Paris) had treated acute leukaemias with aminopterin, but had found that the results were better if this was combined with replacement transfusions. Hetenyi (Hungary) showed that in animals injections of venous blood or cyanide into the nutrient artery of a bone stimulated erythropoiesis. Christiaens and Goudemand (Lille) believed that neonatal jaundice may be influenced by maternal antibodies transmitted by the mother's milk. Bacq and Deronaux (Liége) described the pharmacology of a drug, adrenochrome semicarbazone, which has a lasting effect on the bleeding-time and is neither toxic nor sympathomimetic.

Rheumatic Diseases

This section was opened by Nanna Svartz (Stockholm), who had found that, when all agglutinins against normal sheep-cells are absorbed from rheumatoid arthritis serum, there remains in 90% of such sera an agglutinin to sensitized sheep-cells which is not present in normal serum. This agglutinin is also found in rheumatic joint exudates. She believed a special polysaccharide is involved which is abundant in rheumatic nodules. Layani and his colleagues (Paris) had studied the plasma proteins in Paget's disease without finding any constant abnormality. Layani also discussed sarcomatous degeneration in Paget's disease. Séze, Ordonneau, and Robin (Paris) reviewed the limitations of cortisone in treating rheumatic cases.

Miscellaneous Subjects

The Infectious Diseases Section reviewed ornithosis (Lepine, Paris), typhoid carriers (Knittelfeld, Austria), brucellosis (Maldonado-Allende, Argentina), and gonorrhoea (Durel, Paris). The papers on gastroenterology tended to be more general and historical, but Wiebenga, Jansen, and Verdonck (Leiden) described their gastric biopsy results, and Albot and Bernard-Bruker (Paris) reported their belief that treatment with an emulsion of *B. subtilis* had value in some types of diarrhoea. Neurologists were presented with an exhaustive study of the nervous manifestations of porphyria by Garcin and Lapresle (Paris), with a review of the value and limitations of phenylacetylurea in epilepsy by Euziere and his colleagues (Montpellier), a study of muscular cramps by Roger and Schachter (Marseilles), and with other subjects.

In the Nutrition Section, Markees (Basle) claimed value for the use of cocarboxylase in diabetic coma and other conditions in which blood pyruvic acid is raised; this was doubted by Gilliland (London). Salmon-Malebranche (Paris) stressed again the psychological factor in the aetiology of obesity.

Films

Several good films were shown during the Congress, and among these "The Radiography of the Spine" (Séze, Paris), "The Surgical Treatment of Portal High Blood Pressure" (Santy, Lyons), and "Thrombosis and Embolism" (Waterville, Geneva, and Jurgens, Basle) were notable. These were in a sense documentaries, but the film by Mote (Chicago) broke new ground, showing the great value of A.C.T.H. in controlling recovery from severe burns. Pain, infection, and electrolyte disturbance are all minimized and healing and epithelization hastened.

PRESENT STATUS OF CORTISONE AND A.C.T.H.

DR. PHILIP HENCH IN LONDON

Dr. Philip S. Hench, of the Mayo Clinic, has recently delivered two lectures in London. The first, entitled "Cortisone and A.C.T.H. in Rheumatic Diseases," he gave on October 5 to the Department of Rheumatic Diseases of the West London Hospital. Dr. W. S. C. Copeman was in the chair and members of the Heberden Society attended. Dr. Hench also showed a film illustrating the effects of those hormones on patients with rheumatoid arthritis treated at the Mayo Clinic.

Dr. Hench's second lecture was given at the Royal Society of Medicine, where the attendance was so great—the Barnes Hall being packed and the proceedings relayed to another hall—that the chairman, Professor R. A. McCance, decided that to have a discussion after the lecture was impracticable.

In describing the action of cortisone as used by himself and his colleagues—Drs. E. C. Kendall, C. H. Slocumb, and Howard F. Polley—Dr. Hench said that the hormone did not kill any micro-organism or remove any unknown irritant; what it did was to provide susceptible tissues with a shield-like buffer. It did not, so to speak, put out the fire nor even repair the fire damage, but it did provide a kind of asbestos suit by which the patient was protected. When the suit was removed prematurely the tissues were again subjected to the flame. But once the inflammation was suppressed it could remain suppressed by simple maintenance doses.

Individual tolerance to cortisone and A.C.T.H., said Dr. Hench, varied greatly. Males tolerated the hormone better than females, especially adolescent and menopausal females. Such effects as acneiform eruptions or "round face" might be endured temporarily in view of the need of the patient. Fairly common side-effects were minor alterations of psyche, restlessness, and insomnia. Occasional ones were retention of fluid, hypertrichosis, folliculitis, and transient amenorrhoea. More rare were hypoglycaemic alkalosis, altered libido, retrocervical fat ("buffalo hump"), and increased blood pressure. Spontaneous fractures were rare. There were now more than 3,000 rheumatoid patients in the United States who had received cortisone, and he knew of only four cases of spontaneous fracture in elderly osteoporotic persons. To prevent adverse effects, if prolonged administration was necessary after initial suppressive doses, only the smallest effective maintenance dose should be used. The administrator should be content to suppress symptoms and not necessarily to reduce sedimentation rates.

Some 50 steroids, said Dr. Hench, had been studied with a view to finding substitutes for cortisone. These were all more or less related to cortisone, but apart from "compound F" (which had not yet been synthesized, so far as he knew, though it probably would be in the near future) none of them produced significant effects. Dr. Hench added that cortisone was now priced at 50 dollars a gramme. Supplies were now sufficient to make cortisone available in limited amounts to all approved American hospitals, with growing supplies for foreign medical centres. He had recently seen the first specimen of A.C.T.H. from the pituitary of the Norwegian whale.

In May, 1949, a special preparation—a mixture of compound E and compound F—was given to a severely rheumatoid patient by mouth, and the patient became symptom-free. From this and certain animal experiments it was concluded that cortisone was effective when given by mouth. Cortisone tablets had since been given by Dr. Richard Freyberg, of New York, and by Dr. Hench and his associates in 25 rheumatoid cases with satisfactory results. To their pleasant surprise they found that no larger quantity was needed than when given by intramuscular injection.

After describing the effects of cortisone on rheumatoid arthritis, Dr. Hench turned to some other conditions. Renal lesions were usually not affected, though temporary remission might be afforded. A few cases of chronic ulcerative colitis had been treated; in one of them—arthritis also being present—cortisone was given for 35 days: it brought about complete articular remission, with symptomatic remission of the colitis, which remission had continued for seven months or more after

the end of the treatment. Cases of pulmonary tuberculosis had been treated, with subjective improvement, reduction of sedimentation rates, and improvement of *x*-ray picture of the lungs in some but not in other cases. In cases of tubercular arthritis the sedimentation rates had decreased and the articular symptoms cleared up. But because of the possible inhibiting effect of cortisone and A.C.T.H. on fibroblasts these hormones should be used only as an investigative procedure in the presence of tuberculosis.

A few patients with osteoarthritis had been treated (cortisone was so precious that it was not considered advisable to use it on a relatively benign disease), and considerable relief had been obtained in about half. Cases of acute gouty arthritis had been relieved, sometimes after a single large dose. Remissions in cases of asthma had lasted from one week to five months after discontinuance of the hormone. One important use was in inflammatory diseases of the eye—subacute uveitis, iridocyclitis, and other conditions.

Dr. Hench ended his lecture by saying that, although some of the clinical effects recorded were non-specific, the ability of the hormone to influence markedly a disease process, or even to reverse it, appeared to be group-specific. These hormones had furnished a powerful weapon with which to investigate many problems relating to the aetiology and treatment of a wide variety of diseases. Research workers were at the beginning rather than the end of the road.

Correspondence

Psychology and Science

SIR,—I imagine few scientists, and hardly any psychologists, would accept the definition of science which Dr. Clifford Allen has proposed in his recent letter (*Journal*, September 30, p. 783). "Science," he says, "is only a collection of facts and an attempt to explain them so that we can predict what will occur in certain circumstances." This leaves out what is most distinctive of all science—namely, proof. The attempt to predict what may occur in certain circumstances is more characteristic of the practical applications of science (as in medicine or navigation) than of pure science as such. Certainly, if by adopting a given explanatory theory we succeed in increasing the accuracy of our predictions, that may serve as an additional confirmation of the theory; but not every form of proof, nor even every inductive proof, rests on the verification of predictions. In Kepler's demonstration of the laws of planetary motion and in Harvey's demonstration of the circulation of the blood there is no reference (except as an incidental corollary) to any practical prediction.

It ought perhaps to be added that by proof I mean, not the demonstration of a certainty, but the estimation and comparison of probabilities. Dr. Allen contends that "the theories of Freud are no more fantastic than the theories of Hughlings Jackson" or those of the mathematical physicists. But whether a theory seems fantastic or not has little to do with its final validity. Certainly the more fantastic a theory appears—that is, the more the *a priori* probabilities are against it, and the less readily it can be integrated with conclusions already established—the stronger is the need for high *a posteriori* probabilities in its favour: that at least would be my own view. But many scientists have contended that the role of *a priori* probabilities in empirical proof is so small and dubious that it is safer to neglect them.

An almost perfect model of scientific method (as the psychologist would understand it) is contained in the article by Professor Bradford Hill and Dr. Doll in the same issue of your *Journal* (September 30, p. 739). The psychologist's objection to psychiatric theories, like those cited by Dr. Allen, arises mainly from the fact that, so far, little or no attempt has been made to test them by any rigorous experimental or statistical procedure, such as that which Professor Hill adopts. Of course, many psychiatrists would argue, with Dr. F. Cort (p. 785), that it is better to trust to clinical experience or personal impression than to "cold mathematics." Dr. Allen thinks that we should all be content to regard ourselves as "ignoramuses trying to help our sick fellows." But when an ignoramus tries to help them, he is very apt, like the psychiatrists of an earlier generation, to diagnose mental deficiency by stigmata and head measurements, and to recommend craniotomy for its relief, or, like psychiatrists of the present day, to diagnose neuroticism by paper-and-pencil tests and propose leucotomy or convulsion therapy for a type of patient who, for all the existing evidence has shown, is quite as likely to be injured as alleviated. After all, it was "cold mathematics" that demonstrated the failure of craniotomy and the value and limitations of psychological tests.

But, when all is said, clinical experience and statistical comparisons are by no means incompatible; so why not combine them?—I am, etc.,

London, W.C.1. CYRIL BURT.

SIR,—Dr. F. M. R. Walshe in his distinguished Linacre lecture (*Journal*, August 12, p. 379) has raised criticisms of a fundamental nature for psychology which cannot simply be ignored but call for a reasoned rebuttal if a convincing case is to be made for psychological medicine to take its place as a branch of science. I put it down to the fact that the lecture appeared during the holiday season that his challenge has not been taken up more seriously.

Dr. Walshe has set forth, eloquently and persuasively, two main theses: that psychology is not, and cannot be, a part of "natural science"; and, secondly, that it properly comes under the discipline of historical science as propounded by R. G. Collingwood—and I would like to emphasize the use of the term "science" in this connexion. He makes a distinction between the data of natural science and those of history. The prime method, he says, of natural science is the observation of events, including controlled experiment. History, on the other hand, is concerned with human actions that lie in the past, which have not the quality of sense-data as these are understood in natural science.

If one of Dr. Walshe's patients has an epileptic fit in his consulting-room he has all the sense-data present for an observation according to natural science. Must we assume that a week later, or, for that matter, half an hour later, when the event has passed into history, it has completely changed its character? In considering the occurrence after a lapse of time he will be concerned with "human actions that lie in the past . . . which have not the quality of sense-data as these are understood in natural science." If the answer is that the event, being observed by himself, remains for him a part of natural science, suppose then he is describing the incident to a colleague, is the latter precluded from accepting it as properly scientific but must perforce consider it merely as historical? One can visualize the colleague, weeping, perhaps, like the Walrus and regretting that, while he believed every word Dr. Walshe said, he could not accept his story as scientific but only as history.

The thesis clearly introduces a number of complications, and I would like to ask at this stage if Dr. Walshe considers that psychological events and processes are less "factual" than the events and processes of the external world which make up the data of natural science. He will, I know, be aware that the "facts" or sense-data of the physical world have been subjected to such a nihilistic analysis of late years by philosophers that they could hardly be made more tenuous and abstract. Bertrand Russell, for example, is compelled to go so far as to maintain that when he sees his friend Jones he knows he is only looking at a bundle of "light quanta."[1] On the other hand, to make the distinction less distinct it almost seems as if certain philosophers tend to endow the sense-data of physical science with psychological attributes. It is not so long ago that Eddington, a "natural" scientist, puzzled at the capricious behaviour of the electrons, decided that they must be endowed with free will—a very mysterious mystery indeed, as Damon Runyon would say.

Collingwood's theory of historical method displays, it seems to me, mainly his naivety and bias against psychology, the

latter manifesting itself quite strongly in his autobiography.[2] As Dr. Walshe mentions, Collingwood teaches that "the historian investigating any event in the past makes a distinction between what may be called the outside and the inside of an event. By the outside of the event I mean everything belonging to it which can be described in terms of bodies and their movements. . . . By the inside of an event I mean that in it which can only be described in terms of thought."[3] What does this mean if not that every historical event has a psychological aspect? But Collingwood evidently did not appreciate this even when he emphasized that the cause of an event to a historian means the thought in the mind of the person by whose agency the event came about. He did not proceed beyond "thought" and, in fact, made the incredible affirmation that those actions which are determined by what may be called a man's animal nature, his impulses and appetites, are not properly the subject-matter for history.[4]

It is clear, in fact, that Collingwood's method is not so much a historical science in which psychology should be included but is a psychological method in which history should be comprehended. To consider, for instance, the example quoted by Dr. Walshe from Collingwood: Why did Brutus stab Caesar? Was it from the highest patriotic motives (the "noblest Roman of them all"), was it from mean personal envy, or was it, perhaps, from a combination of both? Who is the right person to answer these questions? Is it the archaeologist or the decipherer of ancient documents? Or is it the trained psychologist experienced in assessing motives from the available evidence?

Dr. Walshe criticizes Bernard Hart's lucid and convincing exposition of psychological medicine as part of natural science on the ground that "the essential data in psychology, as we find it in medicine, are the mental processes behind the façade of the so-called 'observed facts.' It is surely a *non sequitur* to invoke the canons of natural science in this situation." In the name of all the atoms and celestial bodies, why? Is it unscientific of the astronomer to try to get behind the façade of the stars in the heavens or of the physicist to try to penetrate into the processes behind the particles of material things? It is a matter of inference in each case, and accurate inference is an essential element in the scientific method.

When Dr. Walshe declares that it is impossible to generalize about psychology to-day because it has no unity of method or of concept he is stating something that is, unhappily, true. Psychology has not even yet shaken itself free from superstition, theology, and personal predilection, and neither, I regret to say, have many medical psychologists. To maintain, however, that the data of psychology—the events and processes of the mind—are not facts equally with the admitted facts of the natural sciences seems to me to be merely mysticism. If they are admitted to be facts they will be capable of being collated and manipulated according to the true scientific method.

With great respect I suggest that Dr. Walshe has been led off the straight, narrow, and slippery path of valid scientific thinking largely by falling a victim to Collingwood's fallacious teaching on historical "science," based as it is upon a naive and uninformed attitude to psychology. I must add, again with great respect, that I consider it is a fantasy to think that there can be different kinds of sciences, "natural," "historical," and possibly others. There is only one method of science, and accuracy is its watchword.—I am, etc.,

London, W.1. FREDERICK DILLON.

REFERENCES
[1] *The Scientific Outlook*, chap. 3.
[2] *An Autobiography*, chap. 9.
[3] *The Idea of History*, p. 213.
[4] Ibid., p. 216.

Distinction Awards

SIR,—Surely Mr. R. L. Newell has misinterpreted (September 30, p. 783) the main gravamen of Mr. R. S. Murley's letter of September 23, p. 726. I was myself chairman of a meeting of specialists addressed by Lord Moran. The letter convening the meeting gave its object as an opportunity for informal discussion. Only a small minority of consultants attended. Lord Moran after a review of the steps taken regarding distinction awards asked for the immediate formation of a small committee to put forward names for these awards. He indicated that delay in appointing such a committee might be prejudicial to potential recipients. The meeting then proceeded to appoint a committee.

I have since been taken to task by certain of my fellow consultants for my acceptance of this procedure. They say that, while there are many consultants who would not feel justified in giving up time for informal discussion of a subject which has already been very fully discussed formally and informally since the report of the Spens Committee was made public, there is not one who would not wish to be present to register a vote in the appointment of this very important selection committee.

Assuming that the conveners of the meeting knew that this important step was to be taken, they ask why there was no mention of it on the agenda of business.

There has been no question of "whether Lord Moran is right in going round the country addressing meetings of non-teaching consultants," but only whether it is right to press for the immediate appointment of a committee to forward names for awards at badly attended meetings, called ostensibly for the purpose of informal discussion.—I am, etc.,

Sudbury, Suffolk. H. BATHURST NORMAN.

Distinction Declined

SIR,—I find myself unmoved by the pathetic appeal by X in your issue of October 4 (p. 887), and I suggest that he is the victim of confused thinking. As one who declined to complete the questionary submitted to consultants by the Distinction Awards Committee, and who said explicitly that he did not wish to be graded for an award, I received a reply from the secretary to the committee informing me that the committee's terms of reference required it to grade me whether I wished it or not. In due course I was notified that I had been graded for an "A" class distinction award, and thereupon replied that I declined to accept it. It would seem, therefore, that I am still on what X calls "the road to distinction."

My own view has always been that this is no road to distinction, but only the road to a very different thing—namely, the road to a "distinction award." No committee can confer distinction on me, except in the neutral sense that it can "distinguish" me from my brethren by placing me in a salary category. Further, if X has declined to accept the basic sessional payment for which he is eligible, how can he reasonably ask to be allowed to accept what is only a pensionable increment to the basic salary? Can there be an increment to nothing?

I agree with X, however, in thinking that the secrecy which purports to surround the award is a pious figment. Already a patient has asked me whether I know Mr. Y, the brother of the general practitioner who referred him to me, adding that Dr. Y has told him that his surgical brother has just received "the very highest distinction award."—I am, etc.,

Z.

St. Luke's Day

SIR,—On October 18 members of the Christian Church remember with gratitude the work of the most famous member of the medical profession. At this season it is fitting to call attention to the remedies prescribed by Luke for the soul of a sick world. Many of us to-day are willing to admit that the world is sick. There is a growing consensus of opinion that the disease is selfishness complicated by materialism. But proceeding to therapeutics we find wide divergence of views.

All down the centuries of our Christian era men and women have been proving the value of the prescriptions left us by Luke and Paul. To-day thousands are learning that by accepting Christ's standards of truth and love human nature can be changed. Is there any other remedy for the world's sickness?

To-day we may share the optimism of Luke and Paul. Never perfect, but always aiming at Christ's standards, we can be confident of final victory.—I am, etc.,

Banstead. HERBERT CAIGER.

Child Health and the Future

SIR,—As one of those who have been interested in child health for over 40 years—I inaugurated a clinic at the Liverpool Maternity Hospital in December, 1907, after reading Budin's book *Le Nourrisson*—I welcome the interest that paediatrics is now taking in preventive work. Professor Alan Moncrieff in his review (*Journal*, October 7, p. 795) is critical of the present and briefly alludes to the past. In 1904 there occurred in Liverpool in a single week of the year many more deaths, twice as many, from gastro-enteritis as now occur in a whole year. The infantile mortality rate has been reduced to one-fifth; it was, as Professor Moncrieff states, to combat this frightful mortality that the first health visitors were appointed by the local authority, and then infant-welfare clinics were set up. Professor Moncrieff criticizes, and rightly, our present efforts against tuberculosis in childhood. It may, however, be pointed out that in this city deaths from tuberculous meningitis under 15 years of age have fallen from 126 in 1915 to 19 in 1949. Most of this reduction occurred before the introduction of streptomycin. Child mortality—i.e., at ages between 1 and 5 years of age—has been reduced to one-tenth of the 1920 figure.

The improvements in child health, as apart from mortality, have been no less striking. At the beginning of the century the out-patient departments swarmed with cases of rickets, tubercular glands in the neck, congenital syphilis, blepharitis, etc., which are now but rarely seen. As recently as 1941 there were in city hospitals as many as 800 cases of diphtheria; now there are but a dozen or less. Deaths classified as from "external causes" are but one-twelfth of what they were in 1900.

These results constitute an outstanding achievement. Compared with them any defects in present-day practice, such as the doubts expressed, *vide* Professor Moncrieff, by one unnamed M.O.H. concerning the value of breast-feeding, are relatively trivial. That there is still room for improvement is true. Leaders in public health are well aware of that.

Nevertheless the resistant hard core of infant mortality, namely prematurity, has been attacked by local authorities even in the midst of wartime difficulties. The death rate under the heading "congenital defects, prematurity, etc.," of which prematurity is the possibly preventable fraction, is but two-fifths of the 1900 figure. The still-birth rate has also fallen, an occurrence associated with better antenatal care and feeding. A year or so ago on visiting a famous maternity hospital I enquired of the paediatrician what arrangements were made for continuity of care of premature babies after discharge from hospital, and was astonished to find not only that there were none, but that they did not appear even to have been considered. At that time in all the four Liverpool municipal hospitals with maternity units there were prematurity sections; these notified the health visitor in whose area the baby's home lay and she, in return, furnished a report on the home conditions *before* the baby's discharge home. Certainly there may be room for more co-operation of this sort between the hospitals on the one hand and the infant-welfare departments and general practitioners on the other.

As regards breast-feeding, I am unaware of any health visitors who discourage or are lukewarm about it; it would be contrary to all their training. The harm is often done before she calls. Such discouragement may indirectly take place in hospitals; the over-segregation of the mother and infant may have psychological consequences, one of which is the—often voluntary—failure of breast-milk. The ready availability of dried milk may make it easy for the mother, either because she wishes to, or more often because she considers her breast milk is inadequate, in quality or quantity, for her child. In this matter popular views have often to be opposed. I hope that those who teach will continue to emphasize the great advantages of breast-feeding.

The achievements related above were not accidental; they were a well-planned co-ordinated effort. Immunization against diphtheria resulted from the combined work of health visitors, infant-welfare departments and clinics, and school doctors and teachers, under unified direction and greatly helped by Sir Wilson Jameson's broadcasts. We have recently seen the unhappy results of disorganization of the tuberculosis services. The pre-eminence of tuberculosis over other infective conditions as a cause of child deaths is largely due to our national failure to use B.C.G.—only this year available and in limited amount. I welcome the aid of all in combating tuberculosis. Many paediatricians, I know, are keenly interested in its use. If we all pull together we may see results comparable to those achieved in relation to diphtheria. I hope nothing further will be done to disintegrate the preventive services. They are at the moment gravely hampered by inadequate salary scales and a great shortage of health visitors. I welcome Professor Moncrieff's observations on family life as all-important in the life and health of the nation. For a number of years I have lectured to health visitors, D.P.H. students, and others on the possibility of improving the basis of mother-child and family relationships by antenatal and post-natal instruction in the clinics. The basis of knowledge of mental health,[1] which I discussed in 1948, should be laid down in the senior medical student years. This is not adequately done now.

One of the causes of neurosis and delinquency in childhood is parental marital disharmony, and this is what those of us who are engaged in marriage guidance are endeavouring not only to heal but also to prevent. We believe that much of the present breakdown of marriages is preventable. A good family life is the main basis of mental health, and the moments when the woman is most open to advice are before marriage and before the birth of the first, and perhaps second, child. There is as wide a field of useful endeavour in the preservation of mental health opening before us as was given to us at the beginning of this century in relation to physical health. If the health services are to be disintegrated into separate over-specialized services I fear that prevention will gravely suffer.

Professor Moncrieff touches also on problem families. These social problems have been illuminated by the researches of M.O.H.s and their staffs—e.g., Savage, Wofinden, Tomlinson, and others—and the Blacker Committee will shortly produce a report. In about one-third of these families the mother is mentally defective and with them infant mortalities of treble that prevalent in the area often occur. I personally have tried the method of case conferences with the other family social workers, statutory and voluntary, involved. I do not think there is any easy answer to this problem in infant mortality and child ill-health. Does anyone know the answer to this?—I am, etc.,

Liverpool. C. O. STALLYBRASS.

REFERENCE

1 *Publ. Hlth, Lond.*, 1948, 61, 123.

SIR,—I had the great pleasure of hearing Professor Alan Moncrieff deliver his Dawson Williams Prize lecture (*Journal*, October 7, p. 795). His delivery was superb, and the text as published in your issue shows him to be a true master of the English language. As a general practitioner I would like to comment upon what he terms a paradox. He says that it is hard to explain a decline in breast-feeding which has been accompanied by a sensational drop in infant mortality figures. He goes on to say that it is acute respiratory disorders which now present the major difficulties after the newborn period.

Even in 1935 Grulee, Sanford, and Schwartz[1] in a study of morbidity and mortality in 20,000 breast and artificially fed infants found that it was the respiratory disorders which were the most prevalent. Both breast and artificially fed infants became susceptible at 5 months, but the artificially fed infants remained highly susceptible up to 9 months, giving a morbidity rate at that age of twice as much as in the breast-fed, and a mortality rate six times as high. This survey was based on the incidence of such infections as elicited by case histories taken in a welfare centre and refer only to the attack and not to its severity or length.

I have been studying this problem also and find that not only is the incidence of respiratory infections higher in the artificially fed, but that they recover more slowly. For all infections during the first year of life I found that the artificially fed infants required five times as many visits from the family doctor.[2] This surely has great significance and is a reason why we should all pay much *more* than lip-service to breast-

feeding. The common cold, with its dangerous sequelae, spreads, as Professor Moncrieff points out, by contact with the family group. Unfortunately, however, the common cold carries no immunity. On the contrary the immunity seems to work in reverse, and the more times a child catches a cold the more likely he is to catch another soon. If the baby is also slow to recover, then the second infection may come along before the first has entirely cleared up. I can see in this a very strong argument for the encouragement of breast-feeding.

One other comment. It has been stated that dried milks are not *displayed* to the public, but only distributed on the orders of the doctors at the clinics. Recently, when on holiday, I had occasion to call at a food office. As I waited for my emergency card I was forced to look upon a veritable pyramid of dried-milk tins displayed along with orange juice and cod-liver oil in bottles. I am sure that this type of display has the same effect upon the mother as the advertisement upon the hoardings has on the public.—I am, etc.,

York. F. Charlotte Naish.

References

[1] Grulee, C. G., Sanford, H. N., and Schwartz, H., *J. Amer. med. Ass.*, 1935, **104**, 1986.

[2] Naish, F. C., *Lancet*, 1949, **1**, 146.

Sir,—The description of the school health service as given in Professor Moncrieff's paper (*Journal*, October 7, p. 795) is far different from that known to myself. I have been some eighteen years in this service with three different authorities, and also have a more or less intimate knowledge of the systems of many other authorities. The conception that a school medical officer need spend most of his time carrying out routine medical inspections is entirely erroneous. In Liverpool only about 25% of the total of the school medical officers' services is occupied with this work. I quite agree that time would be wasted by such inspections. All that is required is a rapid screening, and then provision made for selected cases to be seen at special clinic sessions. The importance of health education is rightly stressed, and there is surely no better means than the giving of advice to individual parents during the course of these routine examinations.

In consideration of the above, together with actual experience of such a system, I would not endorse the carrying out of these inspections by health visitors. This is not work for which health visitors are qualified, and in consequence their selecting of cases is either on such a wide basis that there is no saving in the time of medical officers or else cases of importance are missed. The field of interest in the school health service is much wider than that of clinical paediatrics, and morbidity and mortality statistics are not adequate yardsticks with which to measure the results. I would recommend to those interested in the work of the school health service the Annual Reports of the Chief Medical Officer of the Ministry of Health: "The Health of the School Child." A study of these reports will reveal that the school health service has steadily progressed and is indeed very different from what it was in 1907–8.—I am, etc.,

Liverpool. G. Stuart Robertson.

Sir,—I very much admire the courage of Professor Alan Moncrieff, and I found his Dawson Williams Prize lecture (*Journal*, October 7, p. 795) most stimulating, as many others must have done. I do feel, however, that I would like to defend the principle of routine examinations, as this seems to be coming in for very heavy criticism at this time. Three years ago I started routine annual examinations of my child patients in order to investigate the value of such a procedure. At the beginning I accepted the conventional theory that the main purpose was to bring to light occult and minor ailments the treatment of which would prevent major disease in the future. If this were the only reason for carrying out physical examinations I would be very inclined to agree with Professor Moncrieff that, although some defects are undoubtedly discovered in this way, and quite a lot of good is done, the immense amount of labour produces only a small harvest. There are, however, other reasons for seeing the growing child at fixed intervals. A routine examination can be regarded as the taking of a cross-section of the child's development, a milestone which in practice gives one a very valuable standard of comparison. In other words, the routine examination can be used not only to discover ailments in the past, but as an instrument to discover ailments in the future.

For example, if a mother brings a child and says that he is not getting on well, is off his food and losing weight, reference to the records of the last routine examination will provide a standard by which to judge the child in his alleged illness. If this same child should provide a positive tuberculin reaction, reference to the records will again show whether there has been fairly recent Mantoux-conversion or whether he has been tuberculin-positive for years. It is to be noted that, if routine examinations are carried out for their possible value in the future, then even the obviously healthy children must be included in the scheme.

The value of the routine examination in providing a standard by which to judge the child in the future does not seem to have received much comment, and I would suggest that the reason for this is because the person who normally carries out routine examinations in our child-health services to-day is a different doctor from the one who is consulted when the child is ill. Having had some experience in the school medical service, I have no hesitation in asserting that the value of a routine examination both to the child, his parents, and the doctor himself is very much greater when that doctor is clinically responsible for the child in health and sickness. The natural corollary of this, of course, is that if routine examinations are to remain, some means must be found whereby they can be performed by the child's own doctor.

There is yet another reason why routine examinations are useful, particularly at the present time when normal practice is carried on at rather a fast tempo. Provided that adequate time is allowed, a routine examination is a very convenient time for discussion with the parent on the child's physical and mental development and any other problems that may occur to the mother. It would be difficult to summon a child and parent to an interview for the purpose of health education, but the routine examination provides a very valuable opportunity for such instruction and advice.

I rather wonder if the present reaction against medical examinations for routine purposes is not largely due to the unsatisfactory way in which school medical examinations are normally carried out. The hopelessly inadequate amount of time available for each child, the frequent lack of privacy, and the fact that the doctor is there to "do" so many units, most of whom he will never see again, are all factors tending towards superficiality and the avoidance of long discussion with the parent. Many parents, aware of these deficiencies, are afraid of holding up the moving belt and so keep valuable information about the child to themselves.

There is one further argument in favour of routine examinations that may be valid in the future, if not to-day. Whilst routine examinations may demonstrate very little disease in children, they also show that only a minority have really perfect physique. It must be admitted that for the most part we are ignorant of the factors preventing perfect health. There are a few obvious cases where an underweight, flabby child is obviously mismanaged at home, but we are all too familiar with the substandard child from the perfect home and the perfect child from a poor home to pretend that we know very much about the neglected study of the *health* of the child. Perhaps in the future it will be possible to measure the degree by which a child falls short of perfection and to prescribe appropriate remedies, in which case routine examinations will be of importance again.—I am, etc.,

Bristol. Norman J. Cook.

"Dramamine" and Sea-sickness

Sir,—In view of Professor J. H. Burn's comments on the use of antihistamine compounds in sea-sickness (*Journal*, September 23, p. 692), some observations of mine on their use in a fleet destroyer may be of interest. About a year ago I became aware of the inadequacy of hyoscine in this condition. Its usefulness appears to be confined to the mild cases, and then only if taken before rough weather is encountered. As a sailor usually believes he will be all right next time, he seldom asks for his

pills until he is feeling really ill, by which time they are of little help to him. The result is they fall into disrepute and few bother to take them. There being no "dramamine" available, I tried the effect of "benadryl." Its superiority over hyoscine was at once apparent and it became very popular, though again no one applied for it until feeling really ill. Many who were completely incapacitated were able to carry on their work as usual, though some complained of drowsiness.

Recently a small supply of dramamine came into my hands, and I was able to compare its effects with benadryl. Here, again, the pills were not taken until the patient was actually feeling ill.

The results were as follows:

Antihistaminic	No. of Cases	Complete Relief	Partial Relief	No Effect
Dramamine	30	10	9	11
Benadryl	30	19	6	5
Total ..	60	29	15	16

Of 17 cases who have tried both compounds at different times, five preferred dramamine, nine benadryl, and three found them equally effective. Drowsiness was complained of by two with dramamine and five with benadryl. No toxic effects were noticed, but it has never been necessary to continue treatment for longer than three days at six-hourly intervals, owing to improvement in the weather.

This is admittedly a small series of cases, but it would appear that benadryl is at least as effective as dramamine, if not more so, which is interesting in view of the ready availability of the former and scarcity of the latter.—I am, etc.,

J. M. PALMER,
Surgeon Lieutenant, R.N.V.R.

SIR,—I have been a very poor sailor all my life, during which time circumstances have taken me across the North Sea twenty times or more. I was invariably sea-sick unless the sea was dead calm. About fifteen years ago I tried hyoscine hydrobromide to help the sea-sickness. It certainly improved matters, as on comparable seas without it I would have been actually sick. As it was, provided I lay still and quite flat the journeys were endurable on a slight sea. If really rough, it appeared to make no difference, and the nausea continued on land up to 48 hours afterwards.

This summer I started the sea journey on hyoscine and went up to breakfast, where I toyed queasily with a grape-fruit; later I was sick. The stewardess provided me with "dramamine," which sent me to sleep for four hours. Then, although the sea was rougher, I got up perfectly well, and enjoyed a dinner of roast duck, ice with whipped cream, and blue cheese. After the holiday the sea was worse on the return journey, but, thanks to dramamine, I was up and present at all meals the entire journey, and next day on shore I was perfectly well.

Personally, I cannot praise dramamine too highly as a sea-sick cure.—I am, etc.,

Birmingham. ENID HOUGHTON.

SIR,—As an inveterate sufferer from sea-sickness, and, like my friend Dr. M. F. Bethell (October 7, p. 836), a recent ship doctor, I would disagree with his conviction that "dramamine" is superior to the hyoscine preparations.

I was asked by the medical superintendent of a shipping line to carry out a trial of this drug, at that time in short supply. In cases of severe sea-sickness I could not repeat the spectacular results claimed by the Americans despite the usual methods to make the sufferers retain the drug. I often found it ineffective or definitely inferior to hyoscine in warding off impending attacks.

In my own case the recommended dose of dramamine was very alarming; a sense of impending doom convinced me that the proof of this pudding lay in the individual. I would agree with Dr. C. Grantham-Hill that there are many individual types of sea-sickness.—I am, etc.,

Chertsey, Surrey. JOHN C. L. ADAMS.

Objective Assessment of Symptoms in Rheumatoid Arthritis

SIR,—Progress in rheumatoid arthritis is difficult to assess, and it is not surprising that clinicians relatively inexperienced in the rheumatic diseases have reported results of treatment with such agents as desoxycorticosterone acetate (D.C.A.) and ascorbic acid that conflict with the findings of specialized rheumatism units.

Steinbrocker's system of defining the stage of disease, the functional class of the patient, and his method of assessing the progress made, have been used with success in following a group of patients at the rheumatism clinics of the Leeds General Infirmary and the Royal Bath Hospital at Harrogate. This system is of use only in assessing clinical change over a period of months, and it is quite unsuitable for assessing such rapid change as may follow the administration of such therapeutic agents as cortisone and A.C.T.H.

Any objective test which will measure clinical change or improvement is of importance. C. E. Quin, R. M. Mason, and J. Knowelden (*Journal*, October 7, p. 810) describe four so-called objective tests. A series of cases of rheumatoid arthritis treated with D.C.A. and ascorbic acid, in which similar tests were performed, was reported last year with negative results.[1] I feel that it is necessary to point out that none of the tests performed are entirely objective, and all with the exception of the "walking test" are difficult to measure accurately. Considering these tests in turn, it will be seen that none are entirely objective.

Joint Tenderness.—This is, of course, a subjective test. Even with the use of the analgesiometer (Kellgren), variable results can be obtained. In performing such a test it is essential that preliminary examination of the patient should show that the tenderness is not varying from day to day or at different times of the day.

Grip Test.—I have used this test on more than a hundred patients, and, if the method of gripping the bag is always the same, consistent results can be obtained in the normal and rheumatoid subject. However, a slight variation in the method of holding the bag produces a considerable alteration in the level of mercury. This can be demonstrated easily by anyone wishing to try it. Again, too, the co-operation of the patient is necessary. It is important that such measurements are taken at the same time of the day and at approximately the same room temperature.

Range of Joint Movement.—I have measured the range of movement of joints in rheumatoid patients who are not receiving active therapy, and a variation of ten degrees was often found from day to day. The range through which a patient will move a joint within the limits of fixed deformity will depend upon muscle spasm and local pain—again, subjective. Temperature has a great influence on muscle spasm, and I have on several occasions seen a joint which was clinically fixed move through forty-five degrees following local heating.

The shoulder-joint is one of the most unsatisfactory joints in the body for accurate measurement. From the article it appears that the angle was measured by one observer before the injection and by a different observer after the injection. Even using skin markings and instrumental aids, the readings of different observers measuring the same joint will show a considerable variation.

Using joint movement as a help in assessing clinical change in rheumatoid arthritis, it is essential to use a joint with a simple movement—e.g., the knee or elbow. Preliminary skin marking and the use of a long-armed goniometer are essential. Comparisons should be made between the range of movement measured, and not the actual limit figures. I cannot see how differences of five or six degrees in the range of shoulder movement can be measured without instrumental aid.

Walking Test.—The key sentence here is, "Walk as quickly as possible," and this functional test must have a subjective element. In discussing this and other similar tests at the spring meeting of the Heberden Society, at Manchester, 1950, I mentioned that the walking test was the one I had found most valuable in practice.

There are certain objective tests available, and I am surprised that Quin and his colleagues have been unable to establish a satisfactory method of measuring joint swelling. The method I employed (again limited to accessible joints like the knee and wrist) was to mark out with silver nitrate the maximal circumference of the joint. This line must completely encircle the limb. Parallel to this line, and at a distance governed by the size of the limb and joint—e.g., 2 in. (5 cm.) for the knee-joint—are drawn two other circumferences, one distal and one proximal. The use of these three measurements gives a satisfactory estimation of joint swelling.

As Lewin and Wassén[2] described joint redness and heat accompanying clinical improvement with D.C.A. and ascorbic acid, skin thermometry was performed on a series of cases,[1] with entirely negative results. This is certainly an objective measurement. Kellgrén and Janus, at the Heberden Society meeting, 1950, showed a method of measuring joint blood flow, and this is also completely objective.

I am making no attempt to discuss the pathological findings, such as eosinophil counts, which are valuable in such investigations. No criticism is offered of the experimental method used, nor of the actual results obtained.—I am, etc.,

London, W.C.1. R. Harris.

References

[1] Hartfall, S. J., and Harris, R., *Lancet*, 1949, **2**, 1202.
[2] Lewin, E., and Wassén, E., ibid., **2**, 993.

Osteoarthritis and Occupation

Sir,—I would like to support Dr. C. W. Buckley's contention (September 23, p. 728) that trauma, especially minor trauma, is an important cause of osteoarthritis. An analysis of the relative occupational incidence, and its effects on knee- and hip-joints in clinics which I attend, tends to confirm this view. In the Sunderland clinic we have a large proportion of miners who work in fairly low coal seams, mostly on their knees or "hunkers," while at the Darlington clinic a considerable number of agricultural workers attend who, as one farmer put it, are "clod-hopping all day." Among the miners osteoarthritis of the knee as against the same condition in the hip occurred in the proportion of twelve to one, while among the agricultural workers the ratio was reversed and there were 14 hip-joint cases as against one knee case. Other trades showed the following figures:

	Hip Cases	*Knee Cases*
Pneumatic tool workers (other than miners)	6	4
Policemen, postmen, gamekeepers	7	3
Tram, bus, and lorry drivers	2	8

This investigation was made in 209 cases. I believe a much wider survey would be of considerable use, especially if shoulder- and elbow-joint cases were included. Most orthopaedic surgeons are impressed by a steady increase of arthritis of these joints following the widespread use of pneumatic tool machinery.—I am, etc.,

Sunderland. W. Grant Waugh.

Sir,—It seems to me that Dr. C. W. Buckley (September 23, p. 728) and Mr. Franklyn Stonham (September 9, p. 629) are at cross purposes. In his paper Dr. Buckley states quite clearly that major trauma is less often a cause of osteoarthritis than microtrauma, which is often of occupational origin. This is perfectly true, but Dr. Buckley's natural habit of understatement has not, on this occasion, had the desired effect and has led Mr. Stonham into battle. The fact of the matter is, in my opinion, that there are two types of osteoarthritis, one of which might be called simply "osteoarthritis" and the other termed "traumatic osteoarthritis."

Simple osteoarthritis is, as Dr. Buckley says, a matter principally of age and stress. It is sometimes found initially in one joint, and is fully described in textbooks (Fletcher, 1947). It gradually spreads to involve other joints, or it may initially appear in several joints at the same time in the same way as it does in osteoarthritis of the spine, which, although it bears the same name, is not the same disease.

Traumatic or monarticular osteoarthritis is a different condition. It is uncommon, and in 500 cases of osteoarthritis was found only 60 times. So far as I know, it is confined to one joint for all time. I have a case of traumatic osteoarthritis of the left knee (due to a motor accident) which I first saw over nineteen years ago in 1931, and the condition is still confined to that one joint; the *x*-ray changes have gradually advanced over the years. Those unusual cases of traumatic osteoarthritis due to meniscectomy have this same characteristic, and may occur in patients of any age. The youngest case in my experience was operated on for a cartilage in 1943 and was then 23 years of age. I lost sight of the patient in 1946, but the condition was unaltered then, so far as clinical and radiological examination could tell.

Mr. Stonham's view that muscle spasm should call for a revision of the diagnosis is not, to me, understandable and is probably brought about by the fact that prostigmin sometimes relieves the muscle spasm in rheumatoid arthritis.

I think it should be mentioned here that the causation of simple osteoarthritis, although unknown, is closely linked with the incidence of obesity and hypertension. Obesity occurs eight times as commonly and hypertension four times as commonly in connexion with osteoarthritis as in an average cross-section of the sick population. It seems that obesity can only really have an effect through increased stress and strain, which amount to the infliction of multiple microtraumata; hypertension is nearly always associated with arteriosclerosis, and the joints are affected in this way. I certainly agree with Mr. Stonham that patients are justified in objecting to wearing callipers and Marsh knee cages.—I am, etc.,

London, W.1. Ernest Fletcher.

References

Fletcher, Ernest (1947). *Medical Disorders of the Locomotor System.*

Medical Students in Prague

Sir,—As one of the participants in the second congress of the I.U.S. I feel that Mr. Diggory (*Journal*, September 30, p. 780) has been somewhat ungracious in his attitude to our Czech hosts. It is unjust to compare the *Hitlerjugend* with the Czech Youth, who suffered horribly under Nazi oppression for six years. These Czech youths extended to us, and to all other students regardless of nationality, creed, or race, a hospitality unrivalled in its warmth. Whatever may be the political inclinations of the student, it is always in the true spirit of British tolerance to listen and discuss with those who hold opposing views. From these discussions we all learned much, and made many friends among the students of 75 nations. For this reason alone the congress has been worth while.

Mr. Diggory has stressed the earnest desire of Czech students for peace. Would it not be a good thing that we British should show them that we are just as anxious in this pursuit, and may not this common desire for peace become a bond of friendship uniting us?—I am, etc.,

London, W.C.1. A. Herdan.

Sir,—As a participant at the I.U.S. Congress in August I was interested in the account of it by Mr. P. L. C. Diggory (*Journal*, September 30, p. 780). There are some factual inaccuracies in his article on which I wish to comment.

The health services in Czechoslovakia differ in several respects from those in this country, but not in the ways Mr. Diggory suggests. Thus the cost of the scheme is borne almost entirely by contributions, assessed in proportion to income from those within the scheme. It is unfortunate that Mr. Diggory did not quote his sources of information. The Czechoslovak National Insurance Act is available in an English translation (Orbis, Prague); it was submitted for consideration at the International Labour Organization (U.N.O.) conference at San Francisco (June, 1948), and the 1949 yearbook of I.L.O. compares the wider benefits of the scheme favourably with our own. Although self-employed persons are still excluded from the sickness insurance part of the scheme, and do not get entirely free treatment, their financial state does not influence the nature of treatment available.

It is hardly surprising that politics should enter into a discussion of the health service, especially if one considers the realms in which conspicuous progress can be readily observed in Czechoslovakia. What we in this country tend to regard as chronic problems in social medicine (notably tuberculosis) are being rapidly solved, new hospitals and health centres are being built, and group practices are encouraged. Compare this with Britain, where not one new sanatorium or health centre will be built in the coming year. I agree with most of Mr. Diggory's actual observations, none of which contradict this assertion, though I saw nothing to suggest that politics enters into medical treatment in the way he implied. I happened, uninvited, to visit two British students being treated as in-patients for a few days

in the Bulovka hospital; the medical and nursing treatment seemed fully comparable with that in this country; in none of the wards did I see any portraits of Stalin (though there was one of Masaryk).

I disagree with Mr. Diggory's allegation that the high living standards and increased educational amenities he describes were achieved at the expense of political discrimination. We saw that the proposals on such things as grants and fees, student sanatoria, wider university entrance and curriculum reform—which our own student organizations N.U.S. and B.M.S.A. have fruitlessly demanded for a number of years—have been achieved in Czechoslovakia, and I think the heavy Marxist trend we observed among students is a result of, rather than a pretext for, the achievements we saw.

The fact that Mr. Diggory omits from his article all reference to the medical faculty conference, which he attended as B.M.S.A. representative, and to the actual policy put forward by the leaders of our own N.U.S. (far less the very objective replies it provoked) leads me to conclude that he is making a purely emotional appeal instead of presenting the facts on the Congress discussions and work of the I.U.S. Throughout his article there is a constant misrepresentation of the feelings and behaviour of the majority of British students present. Thus the gift of £50 worth of medical supplies to the Korean students is referred to as penicillin from the Communist students present; but in fact nearly every British student contributed towards this gift as a token of genuine indignation over the needless destruction of schools and hospitals, of defenceless women and children, from the mass bombing of towns in both North and South Korea. There is little doubt of how the people of Asia regard this feature of the conflict; as a medical student I extend compassion to all who are needlessly giving their lives and blood in Korea.—I am, etc.,

London, W.C.1. S. A. HALL.

Jaundice and Para-aminosalicylic Acid

SIR,—In your issue of September 23 (p. 729) Dr. G. Hurrell reports the occurrence of jaundice in a young woman under treatment with P.A.S., and concludes that it was probably a toxic effect due to the drug. He presumably excluded infective hepatitis as a possible cause because the usual incubation period of that disease was exceeded by the duration of his patient's isolation in hospital—i.e., 35 days before the symptoms of jaundice first appeared.

In this connexion, however, I think it is relevant to refer to an epidemic of 50 cases of infective hepatitis (to be fully reported in due course) that occurred recently in an Oxford college. Here it was fortunately possible to ascertain the two consecutive days on which all the victims almost certainly became infected; and their incubation periods, determined in this way, varied between 24 and 43 days. It seems possible, therefore, that Dr. Hurrell's case was really one of infective hepatitis with a comparatively long incubation period, and that P.A.S. may be exonerated from being the cause of his patient's unpleasant intercurrent illness.

Incidentally, several of my cases also had albuminuria, which was usually slight; and one case during the pre-icteric stage produced an urticarial rash similar to, though not so severe as, the one Dr. Hurrell describes.—I am, etc.,

Oxford. G. A. BALLANCE.

Unabsorbable Sutures

SIR,—Mr. John Howkins (*Journal*, September 16, p. 659) reports a case of uterine sepsis from unabsorbable ligatures used during caesarean section. The following report of the persistence of suture material in the uterus for eight years may be of interest.

A woman, aged 39, was admitted on August 30, 1950, in the 36th week of her third pregnancy. Classical caesarean section was performed for ante-partum haemorrhage in July, 1942, and a lower-segment caesarean section (before the onset of labour) in February, 1945.

She was not in labour on admission, but was complaining of continuous abdominal pain. Foetal parts were easily palpable. A diagnosis of rupture of the uterus was made, and a laparotomy was performed. Both the foetus, in the intact bag of membranes, and the placenta were lying in the peritoneal cavity in front of the uterus, which had ruptured. The rupture had taken place along the whole length of the anterior wall down to the lower segment, and, after the escape of its contents, the uterus contracted, causing wide separation of the torn edges, as can be seen in the illustration. The foetus, which was stillborn, was removed and subtotal hysterectomy performed.

The uterus as it appeared immediately after removal, showing the marked separation of the torn edges. Strands of suture material are seen at A and B. The probe C is lying in the cervical canal. *Inset.*—A loop of the suture material removed from the uterine wall.

Inspection of the uterus showed several strands of suture material along the whole length of both the torn edges. An interesting feature is that the loops were intact, demonstrating that they had cut through the uterine tissues. It has not been possible to confirm the nature of this material, but it looks, however, like silkworm gut or nylon.

—I am, etc.,

Salford, Lancs. E. E. RAWLINGS.

Indications for Globin Insulin

SIR,—The interesting article by Dr. D. W. Pugh (*Journal*, September 16, p. 657) confirms the opinion that globin insulin is successful in mild cases and in older patients. Since the majority of diabetics are over 40 years of age (over 75%) and since about 65% of ambulant patients need 40 units of insulin or less, it is useful in a wide field where its main advantage over other insulins is its simplicity. Dr. Pugh, however, appears to imply that it is not suitable for patients who need more than 40 units of insulin. A high insulin dosage which is more common in, though not confined to, younger patients is, in my experience, not a contraindication to its use, and over 25% of those using G.I. under my supervision do take more than 40 units with success; some indeed have taken quite large doses (80–120 units) for many years.

The "failed globin syndrome" is that of a maladjusted balance between the carbohydrate intake and the absorption of insulin, which causes hypoglycaemia during one part of the 24 hours with diabetic symptoms at another; it is not confined to globin insulin and is typical of P.Z.I. when given alone in ordinary cases. Here there is "diabetes" after breakfast, which may last till mid-afternoon, while insulin reactions occur at night. In the case of globin it is due, I believe, to an idiosyncrasy of certain patients who absorb insulin unusually rapidly so that the insulin acts strongly in the morning and afternoon and has shot its bolt by the evening. Many of these quick absorbers do well on P.Z.I. alone, which brings the blood sugar to normal limits before the midday meal and maintains a steady balance for the rest of the 24 hours. It is always worth trying before reverting to the more complicated method of using a mixture or combination of P.Z.I. and S.I.

One more point: Dr. Pugh gives a dose of G.I. only two-thirds that of the former total dosage of other insulins; in my experience this is not enough, and may account for the greater incidence of the "failed globin syndrome" in his cases.—I am, etc.,

Hove, Sussex. G. M. Wauchope.

Gastric Ulcer and Vagotomy

Sir,—Mr. D. M. Morrissey's finding of two cases of gastric ulceration six months after vagotomy (*Journal*, September 16, p. 651) is interesting and important. However, there is no doubt that palpation of the stomach at the time of the vagotomy, particularly through a transthoracic transphrenic wound, is not a reliable means of excluding gastric ulceration. I see that these two occurred out of seventy-nine cases of vagotomy. Out of seventy-nine cases of partial gastrectomy for duodenal ulcer I would expect to find on carefully examining the specimens one or two stomachs with small gastric ulcers or scars. I believe, therefore, that these two ulcers may have been present as small quiescent impalpable ulcers at the time of vagotomy.

It is important to avoid vagotomy for gastric ulcer. A careful pre-operative gastroscopy is the best safeguard in suitable cases. At operation careful and close inspection of both anterior and posterior surfaces of the lesser curve of the whole stomach is an even better guide to the presence of a small ulcer or scar than palpation.

Despite the possibility that these ulcers may not have developed since the vagotomy, I would still strongly support Mr. Morrissey's contention that vagal section provides no protection against gastric ulceration developing.—I am, etc.,

London, S.W.12. Norman C. Tanner.

Foreign Body in the Rectum

Sir,—A male, aged 50, a sexual pervert, was admitted to hospital with a round-ended bottle, 2½ in. (6.3 cm.) diameter, presenting above the deep anal sphincter. As in the case recorded in the *Journal* (September 16, p. 680), the bottle was impacted between the bones of the lower pelvis, and could not be moved in any direction.

A vertical incision was made through the sphincters, and extraction was effected without difficulty by short midwifery forceps. The sphincter was then repaired, and convalescence was uneventful.—I am, etc.,

Downpatrick, N. Ireland. J. C. Robb.

Sir,—The recent correspondence (*Journal*, September 30, p. 785) on this matter reminds me of an interesting case when I was a young house-surgeon in the out-patient department at the Royal Infirmary, Edinburgh.

A patient came to the department and on being asked his requirements announced that he had "glass in his bottom." A careful survey of that part of his anatomy revealed no wounds, cuts, or abrasions, and on being pressed for further information he announced that it was "inside." I made a rectal examination and found in the rectum a tumbler, inverted and apparently immovable. How to deal with this situation was outside the scope of my knowledge, and I called in my chief, the late Mr. J. W. Dowden, who under a general anaesthetic endeavoured to remove the tumbler by means of various types of forceps, the tips being protected by rubber tubing. He failed completely to move it. Eventually he had to excise the coccyx, and, having done this, was able with great difficulty to remove the tumbler. I remember that after the whole affair was over the patient was asked to explain how this somewhat unusual occurrence had come about. His reply, for what it was worth, was that he had "sat on it in mistake." The tumbler, I recollect, was one about 3 in. (7.6 cm.) in depth by 2½ in. (6.3 cm.) in diameter, and was a medium for advertising a popular brand of table waters.

I remember feeling some gratitude to the unfortunate patient because this occurrence, and one or two other similar cases very much "off the pattern," enabled me to collect a small surgical prize which my surgical knowledge in no way merited.—I am, etc.,

Carlisle. Kenneth Fraser.

Chlorinated Swimming-baths

Sir,—I agree with Dr. A. D. Symons (*Journal*, September 23, p. 728). In my area I instituted a hypochlorite plant and supplied the public baths and the schools with the hypochlorite fluid, and in addition it was available to the public as a disinfectant. During my period as M.O.H. and school medical officer no school was closed on account of epidemics of infectious diseases. I would point out that the dangers of public swimming-baths are more likely to arise from human pollution from all the orifices and spray infection.—I am, etc.,

Southport. S. T. Beggs.

Sir,—Unfortunately views are usually more colourful than facts and consequently get more publicity than they merit. Mr. R. Ogier Ward (*Journal*, September 9, p. 625; see also September 23, p. 728) thinks it is fair to say that to wash out the nose with water of a chlorinated swimming-pool is to invite disaster simply, it seems, because on the three or four occasions he has been swimming in chlorinated water it has given him nasal irritation. Since then, he says, "I have always believed that this is probably one important factor which encourages the spread of poliomyelitis." Of course anyone can believe the earth is flat or anything else, but contributors to scientific journals whose opinions are apt to be mistaken for truths by the lay press and public should surely give more substantial evidence in support of their beliefs than Mr. Ward has done.

In Gosport (population 59,380), where we have had a chlorinated swimming-pool for the past fifteen years, we have only had 18 cases of poliomyelitis during the same period. Perhaps this is just luck, but certainly lends no support to Mr. Ward's belief. It would be interesting and useful if the Ministry of Health would collect and collate the experience of other towns and cities in this respect and publish their findings. It is unwise to let unsubstantiated opinions go unchallenged, particularly when they tend to discredit what we believe are valuable public health precautions.—I am, etc.,

G. W. Fleming,
Gosport. Medical Officer of Health.

Poliomyelitis: Age Incidence

Sir,—One of the most outstanding and puzzling features of the epidemiology of poliomyelitis is the gradual change in age incidence during the last twenty-five years from the first half-decade of life to school age and later. So striking and consistent has this age precession been in all countries that one can confidently predict that nearly half the cases of poliomyelitis in the present epidemic will be in adults. Dr. Simpson Smith's series (September 30, p. 786) showing 60% of cases in children under 6 would seem to be an exception.

There are, however, two factors which tend to lower the age distribution of poliomyelitis in local outbreaks, both of which are probably applicable to this series:

It has been observed many times during outbreaks of poliomyelitis that the age incidence varies with the concentration of populations. This is, of course, true of many other infective diseases, particularly measles, scarlet fever, and whooping-cough, cases being more concentrated in the younger ages in proportion as aggregation of population increases. It is probable that most of Dr. Simpson Smith's cases are drawn from industrial and overcrowded areas.

A change in the age distribution of cases has been noted during the course of practically all epidemics that have been sufficiently well investigated, the younger ages showing a relatively greater proportion of cases early in the epidemic, the older groups later. This series of cases all occurred before September 1, at which date notifications were probably at their peak.

The high proportion of cases in infants (6½%) in this series is most unusual, particularly as the majority of these cases appear to have had severe attacks.—I am, etc.,

Manchester. W. P. SWEETNAM.

Chloralose as Antihistamine

SIR,—I have read with interest Professor J. H. Burn's article (September 23, p. 691). Professor Burn and his co-workers have proved experimentally that a number of drugs—e.g., local anaesthetics, analgesics, and spasmolytics—can exert an antihistamine action. These findings are analogous to my own experimental observations dating back to 1927–8. The aim of these investigations was to study the effect of chloralose on the histamine action on gastric secretion in dogs and on the isolated gut of guinea-pigs. Chloralose is a compound of chloral and glucose and has been widely used as a general anaesthetic in animal experiments and is also known to have a local anaesthetic action. In these experiments it was shown that the spasmodic effect of histamine on the excised gut of guinea-pigs in Ringer's solution could be suppressed by adding chloralose (1:1,000). These experiments were extended to investigate the influence of chloralose on the anaphylactic reaction of the isolated gut of guinea-pigs previously sensitized to horse serum. No anaphylactic response of the excised gut could be obtained in chloralose Ringer's solution. However, after repeated rinsing in Ringer's solution the same piece of gut reacted strongly to renewed addition of 0.5 ml. of horse serum. The antagonistic action of chloralose was confined to histamine and to the anaphylactic reaction. The spasmodic effect of pituitrin and acetylcholine on the isolated gut could not be appreciably suppressed by chloralose.

Since so far none of the known antihistamines is capable of counteracting the gastric secretagogue action of histamine, my above-mentioned experiments on dogs may be of interest. In two dogs with gastric pouch (Pavlov) and in one dog with a permanent gastric fistula, 1.5 g. chloralose in 60 ml. of water was given by stomach tube. Thirty-five minutes later 1 mg. histamine was injected subcutaneously. The experiments revealed the uniform result that histamine gastric secretion can be almost completely suppressed by chloralose. When chloralose was administered by rectum, only the volume of histamine gastric secretion was reduced, but free acid concentration and total acidity were not appreciably influenced. Again the antagonistic action of chloralose was confined to histamine, for neither gastric secretion produced by 200 ml. of 5% alcohol nor the action of pilocarpine on the salivary glands was influenced by chloralose.

From these experiments I concluded that chloralose is a potent antagonist to histamine and is therefore, so far as could be ascertained, the first "antihistamine" described in the literature.—I am, etc.,

London, W.1. A. ELKELES.

REFERENCES

Elkeles, A. *Arch. VerdauKr.*, 1927, **40**, 380.
——— *Z. ImmunForsch.*, 1928, **54**, 471.

Radiology and the Diagnosis of Miliary Tuberculosis

SIR,—I am concerned about the informative article (September 23, p. 702) by Drs. J. L. Emery and J. Lorber. I was amazed to note that out of the 52 cases of miliary tuberculosis, with the diagnosis established at necropsy, only 18 of these showed any radiological evidence. The editorial comment, "It is clear that *x*-ray examination cannot be relied upon for the early diagnosis of miliary tuberculosis," is very disturbing to those of us who in the past have implicitly relied on the radiological diagnosis of this disease.

Frequently, and I feel other observers will agree, these closely packed pin-point foci do not show on the radiograph on account of certain technical *x*-ray factors which are difficult to control. It requires only the very minimum of respiratory movement on the part of the child to blot out the foci completely and show clear and normal lung fields. On many occasions I have found a normal chest in these cases, where an immediate repeat of one or more radiographs with attention to minimal respiratory or other movements have shown the foci clearly. This is a snag which should be brought to the notice of all workers in this field. It is of equal importance that the radiograph should be of the best technical quality, preferably taken with a fine focus, rotating anode tube, and the appropriate kilovoltage and distance. We must be prepared to accept these percentage figures and the skilled interpretation of the radiographs by Dr. Grout, but I should feel more at ease if evidence was forthcoming that such precautions were taken before this method of diagnosis tends to fall into disrepute.—I am, etc.,

Hull. J. E. BANNEN.

Protection of Laboratory Animals

SIR,—I have read with great interest the article by your special correspondent (September 23, p. 724) on Major C. W. Hume's document. Surely the Minister would have power to choose for his board of control persons who would represent with equal fairness the claims of science and the humane treatment of animals.

Is not a more comprehensive Act called for after a lapse of so many years? The numbers of medical students have increased greatly, and is it not advisable to remind all members of the medical profession that there are ethics to be observed towards animals as well as towards each other?—I am, etc.,

Low Fell, Co. Durham. MAY RAW.

Hydrops Foetalis and Rhesus Incompatibility

SIR,—The interesting letter of Dr. R. T. D. Franklin and his colleagues (September 16, p. 680) describes a case of foetal hydrops due to erythroblastosis foetalis which had been produced by incompatibility of the ABO blood groups. Certain features of this case deserve comment since they are at variance with those usually encountered in haemolytic disease due to the rhesus factor.

In the first place the patient was a primigravida, and gave no history of previous transfusion or injection of blood. Secondly, the autopsy report made no mention of splenic abnormality or enlargement; in fact, apart from the liver all the organs appeared to be normal. Thirdly, the degree of tissue oedema was such that a 26-weeks foetus was distended to a size equivalent to that of a full-term infant, the scalp floated on the skull, and the ascites was so marked that the abdomen had to be punctured before the child could be delivered. All these factors are unusual in hydrops due to the rhesus factor.

In my own limited experience, I have twice encountered dystocia due to the size of a hydroptic baby, and in both these cases there was no rhesus incompatibility. On the first occasion I was called to a confinement where the child's head had been delivered with forceps and the shoulders could not be extracted. I found a tense foetal ascites as the cause of the obstruction, and after puncture of the abdomen across the diaphragm an oedematous foetus was delivered. There was no autopsy. The mother, who had had one previous abortion, was found to be blood group A, rhesus positive, with no agglutinins, and W.R. negative. She has subsequently had a normal confinement of a healthy baby. On the other occasion the patient had been booked for her second confinement in hospital on account of hydramnios. A large infant became impacted in the pelvis as an extended breech and embryotomy was necessary before it could be extracted. There was gross oedema, the scalp floated on the cranium, the serous cavities were all distended with effusions, and the placenta was large and pale. The mother was W.R. negative, group O, rhesus negative, without demonstrable antibodies, and the foetus and also the father were rhesus negative.

There is little available information about those cases of hydrops foetalis in which rhesus incompatibility is not to blame, but Potter (1943) has given an excellent clinical description without throwing any light on the aetiology. She records 17 cases of hydrops without erythroblastosis and without splenic enlargement; six of the mothers were primiparas, and six

subsequent pregnancies produced seven normal babies. The blood groups of the parents are not recorded in these cases, but it is unlikely that serological tests were made in an effort to incriminate ABO incompatibility.

Two interesting speculations emerge. Has Dr. Franklin discovered the cause of a significant number of the unexplained cases of foetal hydrops; and is the gloomy prognosis for his patient entirely justified on the evidence?—I am, etc.,

Birmingham. W. G. Mills.

REFERENCE

Potter, E. L., *Amer. J. Obstet. Gynec.*, 1943, **46**, 130.

Should Pregnant Women receive Streptomycin?

Sir,—I read with interest Dr. P. N. Swift's account (*Journal*, September 30, p. 787) of the successful delivery of a live baby to a woman under treatment for tuberculous meningitis. He states that the progress of the infant has been very satisfactory. However, it is too early to be confident that there will be no latent toxic effects from streptomycin. The effects on the vestibular apparatus after large doses of streptomycin are likely to be permanent, and it is obviously impossible to assess these satisfactorily in an infant until at least the stage of walking is reached. In this case the concentration of streptomycin in the placental cord blood was as high as that of the mother, so it would be reasonable to expect considerable toxic effects on the vestibular apparatus of the infant.

This raises the question of the advisability of treating pregnant women with streptomycin. In tuberculous meningitis death would otherwise ensue, so there is definite justification; however, in pulmonary tuberculosis, where there may be alternative methods of treatment, judgment of the advisability of streptomycin therapy should be withheld until it is certain that there will be no delayed toxic effects on the child.—I am, etc.,

Manchester. M. J. Greenberg.

POINTS FROM LETTERS

The Common Cold

Dr. E. Wrigley Braithwaite (Leeds) writes: In 1943 (*Journal*, 2, 433) you published a letter from me in which I made a number of statements about the pathology of the common cold. . . . It only develops when the individual is in a particular emotional state, which can be clearly defined during the course of psycho-analytic treatment. Cold and wet do not cause a common cold. Cold "proneness" disappears completely as a result of successful psychological treatment. The specific factor is psychological; the microbic secondary. I am glad to see that the Common Cold Research Unit has proved by experiment on a large scale that cold and wet do not cause colds. . . . Last year you reported a speaker at the International Congress of Otolaryngology as saying, "The occurrence of the honeymoon cold, that following a domestic row, and that occurring before or during an examination are well known." He gave it as his view that the best prophylactic against the common cold is a state of emotional balance. In your issue of September 16 (p. 662) the reviewer of a book by Dr. T. H. Holmes under the title "The Sensitive Nose" regarded the evidence that emotional states affect the nasal mucous membrane (and the gastric) as beyond dispute.

Treatment of Sea-sickness

Dr. J. H. D. Webster (London, W.1) writes: In the *Aquitania* in the spring of 1926 leaving New York it was quite rough for a few days, and, though sceptical of all remedies then used, I was able to see the most striking effects of the ship surgeon's remedy, which he found cured or prevented sickness in about 99% of all cases. . . . Dr. B. S. Jones's and Dr. Marmaduke Fawkes's letters on the subject, with acidosis as the cause and alkalis as the remedy, are to be found in the *Journal* (1925) **1**, 139, 240. No remedies can be simpler or cheaper. In many North Sea crossings I have found 20 gr. of sodium bicarbonate and 10 gr. of sodium citrate taken before the boat sails, and hourly or two-hourly for two or three times, and on the second day, say, thrice (unless it is very rough), are sufficient to give a comfortable crossing, taking all meals. . . . On a recent trip back from Paris a passenger in the same compartment was quite incapacitated and in a daze, unable to take food, and we found his wife had "doped" him in view of what she thought would be a four hours' crossing from Calais to Dover. They were non-Europeans on a first visit to England. It seems a pity that nervous theories of sickness should now almost obliterate a proved chemical theory, with a simple and almost invariably effective remedy.

Obituary

Sir ERNEST GRAHAM-LITTLE, M.D., F.R.C.P.

Sir Alexander Fleming writes: By the death of Sir Ernest Graham-Little we have lost a great citizen. For 50 years he was in the forefront of dermatology, and there must be very many students of St. Mary's Hospital, like myself, who have blessed him for his straightforward and sensible teaching of skin diseases. In his own field he had few equals in the healing art. But that was only one of his many activities which have been detailed in the obituary notices (*Journal*, October 14). Here I would like to pay tribute to his kindliness. The student or the recently qualified man never went to him in vain for help and advice, and his wide range of interests made his counsel worth while. Everyone who was intimately associated with him will sorrow at his passing. He was a great character, a likeable character, and one who would go to great lengths to uphold what he considered to be right.

Sir JOHN McINTYRE, K.B.E., C.B., M.C., M.B.

Air Vice-Marshal Sir John McIntyre, who was Director of Medical Services, R.A.F., from 1930 to 1935, died in Tunbridge Wells on October 7, aged 70 years.

McIntyre came of Northumbrian stock, his father being in the shipping business in Newcastle. He was educated at Clifton College, and studied medicine at Cambridge University, where he won the Vintner Exhibition to King's College, and St. Mary's Hospital. He graduated B.Ch. in 1906 and M.B. in 1908. After holding a number of resident appointments at St. Mary's Hospital he went into general practice for some years. He joined the R.A.M.C. in 1915 and was awarded the M.C. a year afterwards while on active service. He transferred to the Royal Air Force when it was formed in 1918 and took a permanent commission in 1919. He devoted the rest of his professional career to the new Service.

We are indebted to Sir David Munro, K.C.B., for the following appreciation: John McIntyre became Director of Medical Services, R.A.F., in 1930 (the title is now Director-General of R.A.F. Medical Services). At the time when he came into office the Air Force Medical Service was still in a formative stage. A false move in the relations already established between two older—centuries older—medical services of the Navy and Army, or, even more important, between the leaders of the medical profession, might have meant a loss of ground patiently won by his two predecessors—in particular by Lieutenant-General Sir Matthew Fell. A failure to co-operate successfully with the rank and file of the R.A.F., especially the high-ranking officers in the Air Ministry and the senior Civil Servants, would have had the same effect. John McIntyre made no such false move: the progress of the infant service remained steady under his direction. Before the 1914–18 war McIntyre had been a general practitioner in Croydon, and a very successful one. He was unlikely, therefore, in his administration to be influenced by customs or traditions handed down from the two older Services. Nor was he. His outlook remained fresh, and he was a born administrator. To common sense he added knowledge, a level head, and an even temperament. If anything, he was too coldly logical. Seldom, I imagine, was he ever bested in verbal or written argument, for he was a careful listener, and, having once grasped the essentials of a problem, his judgment was seldom at fault. Had he

chosen to study law rather than medicine, and had he been able to overcome his natural North-country reserve, he might, I believe, have made a notable career at the Bar. If these remarks seem to present John McIntyre as slightly inhuman, the reverse is the truth. He was a staunch friend, and one of the best and most amusing of hosts—until his wife died. They had no children, and after a long and happy married life he was left a lonely man just about the time when he had reached another unhappy landmark, retiring age.

S. ROODHOUSE GLOYNE, M.D.

Dr. Cecilia Shiskin writes: I should like to add to what has already been published (October 7, p. 841) my tribute to the memory of the late Dr. Stephen Roodhouse Gloyne, whose passing has saddened all who were privileged to know him. I had the good fortune to work in his department at the London Chest Hospital for a number of years. He was not only the expert pathologist who taught and guided his staff, but he also stimulated them in their work. He radiated a warmth and friendliness that made working with him a real pleasure. He took a fatherly interest in each one of us and our personal affairs, so that we felt we were members of one happy family. His kindliness embraced all connected with the hospital—the nurses, the domestic staff, and the patients. When the hospital was bombed in 1941 Dr. Gloyne transported some of the patients to their homes in his own car and saw that they were comfortably placed. He maintained contacts with many former residents of the hospital who came from the Dominions. All sought his guidance and appreciated his advice. The morning-coffee interval afforded a pleasant break, during which Dr. Gloyne would expatiate expertly on a wide range of subjects—music, archaeology, history, and even the culinary art. He enriched the lives of those who were privileged to be associated with him. Our heartfelt sympathy goes out to his widow, his daughter, and his son and family.

Dr. FRANCIS KENNETH KERR, who was in general practice in Leith for 46 years, died in Edinburgh on August 15 in his 73rd year. He was educated at Daniel Stewart's College, and he spent two years in a merchant's office before taking up the study of medicine at Edinburgh University. He graduated M.B., Ch.B. in 1900. His enterprising and adventurous nature was exemplified by his volunteering for service in the South African War as a civil surgeon. For his services in that campaign he received the Queen's Medal with four bars. On returning to civilian life he practised in Cumberland for two years and then moved to Leith in 1904. He was appointed clinical assistant in the *x*-ray department of the Edinburgh Royal Infirmary, and later he took charge of the *x*-ray and electrical department of the Leith Hospital for seven years. In the first world war he served with great distinction in France—where he was awarded the M.C. for conspicuous gallantry in "steadying troops under heavy and accurate hostile fire"—Gallipoli and Salonika. In 1919 he was made consulting physician to troops in Turkey and in the Army of the Black Sea. He attained the rank of lieutenant-colonel and was elected an esquire of the Order of St. John of Jerusalem for his work in the Near East. He resumed practice in Leith after he was demobilized, and in the course of time held many local medical appointments, including membership of the board of management of the Leith Hospital, in the work of which he took an active and lifelong interest. He was a keen member of the British Medical Association and took a leading part in the activities of the local division, both in connexion with the introduction of the National Health Insurance Act and the National Health Service Act. In spite of an inherently modest disposition he was an incisive speaker, with a definite gift of getting down to essentials. Many members of the Edinburgh and South-east of Scotland Branch of the B.M.A. have happy memories of the day when, as president of the Branch, he entertained the members to an excursion to the Island of Inchcolm in the Firth of Forth. He was a representative of the City of Edinburgh Division at a number of Annual Meetings, and a member of the Insurance Acts Committee for some years. He was also a member of the Edinburgh Insurance Committee and of the Panel Committee. He found relaxation from his professional work in amateur acting, football, and swimming. As a practitioner his conscientiousness, ability, and kindness endeared him to his patients, and their sympathy, with those of his colleagues and friends in Edinburgh, will be extended to his widow.—R. W. C.

Dr. ARTHUR WILLIAMSON BRODRIBB, for many years physician to the Royal East Sussex Hospital, died at St. Leonards-on-Sea on September 16 at the age of 71. He studied medicine at Oxford and St. Bartholomew's Hospital, and graduated M.B., B.Chir. in 1905. He joined his father in general practice in Hastings a year later, and remained in this practice all his life, except for a time in the first world war when he was a captain in the R.A.M.C. Arthur Brodribb came of a line of doctors, traceable from about 1800 (and still continuing in his eldest son). He was held in high esteem by his colleagues, and was for 38 years physician to the Royal East Sussex Hospital, being a senior member of the staff for much of this time. He took an active part in the affairs of the town, having been at one time a town councillor and later a J.P. It might be suspected that this was due to pressure from without rather than love of office, since he disliked publicity. His hobbies were gardening and carpentry; and in his active days he was a keen footballer and golfer, being chairman of local clubs in both these branches of sport. It was, however, as a family doctor that Brodribb was supreme, and here he had a touch all his own. He did not appear ambitious to amass a very large practice, but to his patients he gave all that he had of skill, care, and friendship, and they repaid him with their devotion. Thus was established a bond which made him, in their eyes, irreplaceable. He had a quiet voice and courtly bearing—the right sort of bedside manner. The last war came at a time when he might otherwise have thought of easing off: instead, his work was much increased, in conditions which were difficult and often dangerous. The National Health Service also was most uncongenial to one cast in his mould, and after a brief trial he withdrew from it. So he was latterly a tired man; but those who knew him at his best saw something which is not taught in the schools and is now seldom found anywhere.—C. M. C.

Dr. ANDREW EDGAR STRUTHERS, of Paisley, died suddenly on September 16 while on holiday in Arran. It was known to all his colleagues that, since a coronary thrombosis fifteen years ago, he was sensibly and realistically carrying on his daily round and a full and active public life with characteristic fortitude and good humour. Struthers graduated M.B., Ch.B. at Glasgow University in 1910, and started practice in Paisley in 1919 after service in the Navy in the first world war. Before that war he had a short but intensive experience of practice in Coatbridge. Throughout all his years in Paisley he was associated with the Royal Alexandra Infirmary, and he applied his scientific and well-ordered mind diligently and earnestly to his work as physician there. In the public life of the town he was an enthusiastic member of the learned societies and was a past president of the Paisley Burns Club. He was much in demand as an after-dinner speaker, and his original and independent habit of thought made him a most entertaining and provocative raconteur. He was from 1922–45 secretary of the Renfrewshire and Buteshire Division of the B.M.A. He was also a representative on the Scottish Committee. He held many public appointments, including that of honorary secretary of the local medical committee, and he was the area medical officer under the Factory Acts. His pleasing nature and cultivated mind endeared him to a large and appreciative number of patients. Paisley has lost a sound physician and an independent and outstanding personality. His wife predeceased him a few years ago. Sincere sympathy is extended to his only daughter.—J. W. H.

Dr. Daniel Charles Edington died at his home in Penrith on September 23. He was born in 1865, and received his education at the Edinburgh Royal Academy. He commenced his career as a chemist at the Edinburgh Royal Infirmary, but later he decided to study medicine and graduated M.B., C.M. in 1892, proceeding M.D. in 1901. After holding posts at the Royal Infirmary, including that of assistant to the professor of clinical medicine, he was for a short time in practice in Bridge of Allan and also Clackmannanshire before moving to Penrith in 1895, where he continued in active practice till his retirement in 1945. In his earlier years he was a man of catholic tastes and wide interests in sport, music, the theatre, and masonry. He was immersed in medical politics from the days of the heated controversy in the profession over the first National Health Insurance Act, and his level-headedness and clear vision helped to smooth over some of the local difficulties which occurred throughout Cumberland at that time. During the 1914–18 war, despite the departure of his partner to war service, he took on the additional work of medical officer to the Red Cross hospitals in Penrith with enthusiasm and zest. In recognition of his services he was made a life member of the B.R.C.S. His wise counsel was greatly appreciated by his colleagues in this area, and he was for many years chairman of the Cumberland Panel Committee and a member of the Cumberland Insurance Committee. A keen member of the B.M.A. from the outset of his career, he was president of the Border Counties Branch in 1922–3, chairman of the English Division in 1926–7, and chairman of the Cumberland Division in 1938–9. He will be remembered, however, for his fine clinical skill, an eager, receptive mind, a kindly heart, a fund of common sense, and a clear appreciation of his patient as a personality. He will long be mourned by a multitude of Cumbrians, to whom for over 50 years he rendered service tinged with humanity, and by his widow and two sons, to whom we render our sympathy.—J. S.

Dr. William Lowson, who practised in Tamworth for over forty years, died on September 27 at Tamworth aged 78 years. Lowson studied medicine at University College, Dundee, and University College, London, graduating M.B., Ch.B. (St. Andrews) in 1902. After holding a number of resident hospital appointments he came to Tamworth in 1909 as partner to the late Dr. Fausset. He was largely responsible for the formation in 1911 of the public medical service for Tamworth, and acted as its secretary and treasurer until 1947. For many years he was medical officer of health to the Tamworth Rural District Council and the medical superintendent of the Tamworth Isolation Hospital. He was also police surgeon and, during the last war, medical superintendent of Tamworth Infirmary. He was a member of the panel committees for both Staffordshire and Warwickshire, and served on the general and house committees of the Tamworth Hospital until the introduction of the Health Service in 1948. Lowson joined the B.M.A. in 1904, and represented the Nuneaton and Tamworth Division at the Annual Representative meetings for most years from 1923 until 1939. He was chairman of the Division for the 1925–6 session. A keen golfer, he was the captain of the Tamworth Golf Club, and was subsequently elected its president. The sympathy of all who knew Dr. Lowson goes to his widow in her bereavement.—D. S. P.

P. A. V. B. writes: The passing of William Lowson has brought a great sense of loss to his medical and lay friends. He had gained a reputation for his competence, integrity, and his dislike of the sham and meretricious. To those who did not know him well his austere manner was often awe-inspiring, but to those of us who were privileged to be his colleagues that manner was only a very thin disguise worn by a somewhat shy man who possessed a large store of human kindliness and a great sense of quiet humour. He was a staunch friend, and his advice, born of sound common sense, allied to a clear head and keen vision—whether given privately or at a conference—was always proved by time to be right. These qualities endeared him to his patients, and there are many who will mourn him.

Dr. Harold Balme writes: Absence from England during the past month has prevented me from hearing sooner of the death of my friend and former colleague, Edward Gillespie, but I would like to add my tribute to the fine appreciation by Dr. Hadfield which appeared in the *Journal* (September 16, p. 684). At the outbreak of the last war it fell to my lot to become medical superintendent of the Haymeads E.M.S. Hospital at Bishop's Stortford, the medical and surgical staff of which was largely drawn from the Prince of Wales Hospital, Tottenham. The buildings had previously been used as a poor law institution, and the task of converting it into an acute general hospital, capable of receiving all types of medical and surgical cases and of providing teaching facilities for the keen staff of young residents transferred from the London Hospital, demanded detailed preparation, careful organization, and expert hospital practice. In all these matters Gillespie made a notable contribution. His rugged individualism, independence of thought and expression, and fine surgical judgment and technique made an impression on every member of the staff, and I, personally, can never forget the splendid loyalty and wise counsel which I always received from him during those early, difficult years of the war. It was thanks to his influence and that of his confrères that the Haymeads medical staff became welded together into so happy and united a group, and it is a melancholy fact that already three of the most outstanding of them—Burton Wood, Robert Klaber, and Edward Gillespie—have now passed over to the great majority.

Medico-Legal

CLAIMS AGAINST HOSPITALS: A DIFFERENCE OF LAW

[From Our Medico-Legal Correspondent]

Three recent actions against hospitals illustrate the difference between the Scots and the English law in regard to the liability of a hospital. In the first of these[1] a girl of 5 was having her tonsils removed at the Glasgow Victoria Infirmary, and by some mishap sustained a burn of the cheek which left a disfiguring scar. The cause alleged by the father was a hot gag. The board of management pleaded that they had provided a proper, sufficient, and adequately trained staff, and that under the Public Health (Scotland) Act, 1897, they were not liable for any irregularity committed by their officers in the execution of that Act. Lord Strachan, dismissing the action as irrelevant, held that the board was not liable for the actions of a nurse in her professional capacity, and that the National Health Service (Scotland) Act had made no difference in the common law.

In the second case,[2] also in Scotland, a father claimed damages for injuries to a newborn infant whose feet and legs, it was alleged, had been badly burnt in front of an open fire by the negligence of a nurse at the Henderson Memorial Nursing Home, Wick. The board maintained that the nurse had performed her duties competently, and also that it had acted in the bona-fide execution of its duties under the National Health Service (Scotland) Act. Lord Strachan held on the facts of this case also that the board was exempt from liability for any negligence of its own.

In the third case,[3] an English one heard at Leeds Assizes, a girl of 12, a promising pianist, was treated by radium for a birthmark on her right arm and developed a contracture during the after-treatment, so that her forearm was grossly and permanently disfigured. Mr. Justice Croom-Johnson dismissed the action against the radiologist, Dr. Frank Ellis, but was satisfied that the house-surgeon had been negligent, and held that the Ministry of Health was liable as that officer's principal. He awarded £5,000 damages to the girl and £51 4s. special damages to her father.

The reason for the divergence between Scots and English law is that the liability of hospital authorities is based on the common law and not on statute. Both the Scottish and the

English National Health Service Acts provide that the regional boards shall be liable in cases in which hospital governors would have been liable before, and that liability has been transferred to the Minister in England and the Secretary of State for Scotland by the Crown Proceedings Act, 1947. But neither Act has altered the common law as to the liability of the responsible authority. The divergence dates from certain *obiter dicta* in Hillyer's case[4] in England in 1904 to the effect that hospital governors were not liable for the negligence of their staff in matters of professional skill. These *dicta* were in England taken to state the law correctly until the decision of the Court of Appeal in the Essex radiographer case.[5] In that case it was held that hospital governors were liable for the negligence of medical auxiliaries and probably for that of medically qualified employees also. This has been confirmed by later English decisions. However, as Scottish judges have been at pains to emphasize, the development of the English common law does not bind the Scottish courts, which have continued to follow Hillyer's case ever since.

[1] *Scotsman*, May 5, June 10, 1950.
[2] Ibid., June 16, 1950.
[3] *Yorkshire Post*, July 5, 1950.
[4] *Hillyer* v. *Governors of St. Bartholomew's Hospital*, 1904, 2 K.B. 602.
[5] *Gold* v. *Essex County Council*, 1942, 2 K.B. 293.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Horace Basil Barlow, M.B., B.Chir., has been elected to a Research Fellowship at Trinity College for research in physiology.

UNIVERSITY OF DURHAM

At a Congregation held on September 30 the Diploma in Public Health was granted to W. B. A. Smyth.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examination indicated:

FINAL M.B., CH.B.—*Part I*: E. D. Falla, M. N. Harrison, F. B. Hartley, H. Holden, J. Hosker, G. Ingram, E. M. Jackson-Moore, D. E. Phillips, W. A. Weston.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

At a meeting of the Royal Faculty of Physicians and Surgeons of Glasgow held on October 2, with the President, Dr. W. R. Snodgrass, in the chair, the following were admitted Fellows of Faculty *qua* Physician: J. D. H. Bankier, A. Meiklejohn, M. Mousiquddin.

A new 16-mm. sound film entitled "Oxygen Therapy" has been produced for medical, nursing, and other professional audiences by Kinocrat Films Ltd. for Oxygenaire Ltd. The film runs for 35 minutes and is in two parts. Part I covers the history of the clinical use of oxygen, depicts the physiological aspects of oxygen in the lungs, blood stream, and blood plasma, and explains the symptoms and classifies the main types of anoxia. Part II demonstrates the techniques of oxygen administration by face-masks, oxygen tents, etc., to infants, children, and adults, and shows in detail the construction of the latest forms of oxygen therapy equipment. Other essential factors in oxygen therapy, such as various fire precautions to take, are also included in this section. Many sequences were filmed at the Westminster and Queen Charlotte's Hospitals and the Hospital for Sick Children, Great Ormond Street, with the assistance of the medical staff. Arrangements for borrowing the film can be made by communicating with Oxygenaire (London), Ltd., 8, Duke Street, Wigmore Street, London, W.1.

No. 39

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended September 30.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.
Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.
A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1950 (a)	(b)	(c)	(d)	(e)	1949 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Meningococcal infection	25	—	17	1	—	25	3	14	1	—
Deaths		—	1				1	—		
Diphtheria	50	4	16	2	3	76	8	21	2	7
Deaths	—	—	—	—	—	1	—	—	—	—
Dysentery	187	8	127	1	2	163	24	68	1	6
Deaths		—			—				—	—
Encephalitis, acute	8	1	—		—	1	—	—	—	—
Deaths		—		1			1			
Erysipelas			23	8	2			22	3	2
Deaths							—			
Infective enteritis or diarrhoea under 2 years				22	14				120	
Deaths	5		8	—	2	34	3	8	7	6
Measles*	2,963	217	146	43	43	780	40	27	51	45
Deaths†		—	—	—	—			—	—	—
Ophthalmia neonatorum	44	7	8		—	39	5	6	—	—
Deaths										
Paratyphoid fever	11	2	—	1 (B)	1	24	1	1 (A)	3 (B)	1 (B)
								10 (B)		
Deaths	—		—		—	1	—	—	—	—
Pneumonia, influenzal	281	13	7		1	313	16	1	3	2
Deaths (from influenza)‡	6	—	2	—	—	4	—	—	—	1
Pneumonia, primary			126	¶				139	15	
Deaths	120	13		4	8	94	15		5	7
Poliomyelitis, acute	331	16	56	5	10	357	44	7	—	1
Deaths§	17	—		—		23	4			
Puerperal fever			4		—		—	8		
Deaths										
Puerperal pyrexia‖	88	7	8		—	104	8	7	—	5
Deaths							—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	937	47	209	40	54	1,305	112	204	96	104
Deaths†		—	—	—	—			—	—	—
Smallpox	—	—	—		—	—	—	—	—	—
Deaths					—				—	—
Typhoid fever	7	1	1	1	—	12	4	1	2	—
Deaths	—	—	—		—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Whooping-cough	2,616	225	201	69	29	956	43	52	66	65
Deaths	2	—	1	1	—	2	—	1	1	2
Deaths (0–1 year)	218	30	42	14	5	230	27	41	27	16
Deaths (excluding stillbirths)	4,282	680	589	160	114	3,972	602	524	166	107
Annual death rate (per 1,000 persons living)			11·8					10·5	10·3	
Live births	7,414	1205	876	446	213	7,738	1213	899	347	236
Annual rate per 1,000 persons living			17·6					18·0	21·5	
Stillbirths	180	25	23			184	25	20		
Rate per 1,000 total births (including stillborn)			26					22		

* Measles is not notifiable in Scotland, and the returns are therefore an approximation only.
† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.
‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.
§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.
‖ Includes puerperal fever for England and Wales and Eire.
¶ Primary pneumonia no longer notifiable in Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

Notifications of poliomyelitis in the week ending October 7 were: paralytic, 241 (222); non-paralytic, 112 (109); total, 353 (331). The figures for the previous week are in parentheses.

Total uncorrected notifications for 1950 up to and including the week under review were 6,704. The corresponding figures for 1947, 1948, and 1949 were 7,094, 1,735, and 4,015 respectively.

The chief increases compared with the preceding week were in Devon 6, Gloucester 10, and Stafford 11. Decreases were generally distributed in small numbers. Non-paralytic cases in the week under review formed 23.5% of the total.

Compared with the week before, there was an increase in total notifications of 22—all except 3 of the paralytic type. This small rise in incidence is disappointing in view of the decreases in previous weeks, but there is reason to expect that the incidence will decline normally in the weeks to come to the lower levels of winter.

Discussion of Table

In *England and Wales* there were increases in the number of notifications of measles 290, scarlet fever 166; decreases were recorded for whooping-cough 319 and acute poliomyelitis 88.

A small rise in the incidence of scarlet fever occurred in all regions of the country. The largest rises in the number of notifications of measles were Lancashire 54 and Derbyshire 49. The notifications of diphtheria were 12 more than in the preceding week, the largest rises being Yorkshire West Riding 7, Durham 6, and Warwickshire 4. The largest falls in the incidence of whooping-cough were: Essex 74, Surrey 47, Yorkshire West Riding 39, and Gloucestershire 36.

A rise of 17 was recorded in the number of notifications of dysentery. The chief centres of infection were: Lancashire 61 (Bury C.B. 15); Leicestershire 25 (Leicester C.B. 25); Yorkshire West Riding 21; Surrey 13 (Surbiton M.B. 12).

The largest returns for acute poliomyelitis were: Lancashire 30 (Liverpool C.B. 10, Manchester C.B. 9); Yorkshire West Riding 29 (Leeds C.B. 6, Sheffield C.B. 6); Gloucestershire 21 (Bristol C.B. 18); Kent 17; London 16; Lincolnshire 16; Warwickshire 15 (Birmingham C.B. 13); Devonshire 13; Durham 12; Staffordshire 11 (Wolverhampton C.B. 5); Middlesex 10.

In *Scotland* the chief variations in the trends of infectious diseases were increases of scarlet fever 75 and measles 49. The rise in the incidence of scarlet fever occurred mainly in the western area, where the notifications were 60 more than in the preceding week, and an increase of 27 was reported from Glasgow. The largest number of notifications of dysentery were those from the cities of Glasgow 61, Dumfries 22, Edinburgh 11, and from Stirling county 11. The largest returns of acute poliomyelitis were: Glasgow 10, Dundee 6, Fife county 5, and Ayr county 4.

In *Eire* there was a decrease of 13 in the number of notifications of scarlet fever. A decrease of 14 occurred in the number of notifications of whooping-cough in Dublin C.B., but a slight rise occurred in the remainder of the country.

In *Northern Ireland* the chief feature of the returns was a rise of 12 in the notifications of whooping-cough. The largest returns of acute poliomyelitis were Armagh county 3, Antrim county 2, and Down county 2.

Quarterly Returns for England and Wales

The birth rate for the second quarter of this year was 16.7 per 1,000 total population; this was 2.1 below the average rate for the five preceding second quarters. The infant mortality rate, 28 per 1,000 live births, and the stillbirth rate, 22.5 per 1,000 total live and stillbirths, were the lowest rates ever recorded for a June quarter. The general death rate was 11.1 per 1,000, being 0.1 above the rate for the corresponding quarter of last year and 0.5 above the average for the second quarters of 1944–8. There were 71 deaths attributed to acute poliomyelitis. People married numbered 161,082. This number was 38,084 below the average of the second quarters of the five preceding years.

Week Ending October 7

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,064, whooping-cough 2,445, diphtheria 40, measles 3,914, acute pneumonia 351, acute poliomyelitis 353, dysentery 187, paratyphoid fever 11, and typhoid fever 10.

Medical News

Visitor to Copenhagen

Dr. W. W. Mushin, of the Department of Anaesthetics, Welsh National School of Medicine, is soon to visit Copenhagen for three weeks to take charge of the anaesthesiology centre there. The invitation comes from the World Health Organization. There are about 20 W.H.O. Fellows from various European countries attending the centre. Until now the centre has been in the charge of anaesthetists from the U.S.A.

Honorary Medal

At a meeting of the council of the Royal College of Surgeons on October 12, with Sir Cecil Wakeley, president, in the chair, the Honorary Medal of the College was presented to Lord Webb-Johnson "in recognition of his many generous acts and continued labours in the interest of the College during his eight years of presidency."

Chelsea Clinical Society

The first ordinary meeting of the fifty-fourth session was held on October 10 at the South Kensington Hotel, with the new president, Mr. Geoffrey Parker, in the chair. There was a discussion on "Plastic Surgery and the Arts," which was opened by Mr. Henry Blake, F.R.C.S., followed by Mr. Adrian Hill, R.O.I.

Register of Speech Therapists

The names, addresses, and qualifications of speech therapists are listed in the *National Register of Medical Auxiliary Services (Speech Therapists)*, the eighth edition of which has recently been published. Medical practitioners may obtain a copy free on application to the Registrar, Board of Registration of Medical Auxiliaries, B.M.A. House, Tavistock Square, London, W.C.1.

Mountain Air for Asthma

Twelve London school-children suffering from asthma left on October 10 to spend six months in Switzerland as the guests of the Swiss Economic Council. The whole cost is borne by the council, which hopes later to send children from other parts of Britain.

32nd British General Hospital

A successful reunion dinner of the 32nd British General Hospital was held at Birmingham on September 30, Dr. J. F. Wilde presiding. Next year this reunion dinner will be held at the same time and place on the last Saturday in September. Inquiries should be addressed to Mr. W. C. Marsh, 126, Cob Lane, Bournville, Birmingham, 30.

Death Certificates

Under regulations that come into operation on November 1 certain notices of death have been altered to bring them into conformity with the death certificate in general use. The notices are those given under the Mental Deficiency Regulations, 1948, the National Health Service (Emergency Treatment) Regulations, 1948, and the Mental Treatment Rules, 1948.

International Course in Audiology

A course of instruction in audiology was held in Stockholm under the chairmanship of Professor Gunnar Holmgren on September 11–20. The first of its kind ever to be held, this "International Course in Audiology" was opened by H.R.H. Princess Sibylla of Sweden in the presence of 258 participants, of whom 34 came from Great Britain. On the opening morning there were introductory lectures by Professor Holmgren, Dr. Julius Lempert, and Mr. Terence Cawthorne. In all, 24 countries were represented, and the 258 doctors attending included 41 teachers from 13 countries. The course of instruction was divided into lectures in four parallel series, there being some 80 lectures in all, and five practical courses or seminars. These were on audiometry and hearing-aids, hard-of-hearing children, basic audiology, and temporal bone surgery, with special reference to the fenestration operation. They were so arranged that each participant could attend two practical courses each day in addition to three lectures. Films, demonstrations at the Royal Institute of Technology, and demonstrations of operations by Professor Torsten Skoog and Dr. Paul Frenckner at the Karolinska and the Southern Hospitals were also arranged. There was also a visit to the new ear, nose, and throat clinic at Uppsala, which is under the direction of Professor C. O. Nylen. Both teachers and pupils gained much from the course, which proved to be very popular, and plans for another are already being considered.

Royal Academy of Medicine in Ireland

The following officers of the Royal Academy of Medicine in Ireland were elected at the annual general meeting of the Academy: president, Dr. E. T. Freeman; general secretary and treasurer, Professor T. Percy C. Kirkpatrick; secretary for foreign correspondence, Mr. William Doolin.

Chartered Society of Physiotherapy

Professor J. Whillis has been elected to the chairmanship of the council of the Chartered Society of Physiotherapy, in succession to Dr. W. S. C. Copeman, who, owing to pressure of work, has retired from the office after serving for five years.

Dr. Philip Hench's Visit to Britain

Dr. Philip Hench and Mrs. Hench have been visiting Britain at the invitation of the Royal Society of Medicine, the Nuffield Foundation, and the Ciba Foundation. The purpose of the visit is to enable Dr. Hench to discuss the development of cortisone and A.C.T.H. therapy with doctors in this country. On October 10, when Dr. Hench addressed a crowded meeting of the Royal Society of Medicine (see p. 942), the president of the Society, Lord Webb-Johnson, and Lady Webb-Johnson entertained Dr. and Mrs. Hench and other distinguished guests to dinner in the council room. The dinner was informal, but a speech of welcome was given by the president. Sir Henry Dale proposed the health of Dr. Hench, who replied.

Wills

Dr. Ronald Grey Gordon, physician to the Royal United Hospital, Bath, and formerly chairman of the Journal Committee of the B.M.A., left £13,587. Professor Harold John Hutchens, formerly Heath professor of comparative pathology and bacteriology, University of Durham, left £18,621. Dr. Sydney Henning Belfrage, formerly medical inspector of the Divorce Registry, left £11,911. Dr. John Lindsay, of Hebburn, Co. Durham, left £25,612.

COMING EVENTS

West Midlands Physicians' Association

A meeting will be held on Saturday, October 21, to inaugurate the West Midlands Physicians' Association. The Clinical Section will be held at Selly Oak Hospital, Birmingham, at 11 a.m., and the afternoon session will be devoted to general and scientific business and will be held in the medical school of the University of Birmingham at 2.15 p.m.

Professional Nurses and Midwives Conference

The 35th Annual Professional Nurses and Midwives Conference will be held at the Seymour Hall, London, W.1, from October 23 to 27 under the presidency of the Viscount Addison, with, as his vice-presidents, the President of the Royal College of Surgeons, Surgeon Rear-Admiral Sir Cecil Wakeley, and the Right Hon. Walter Elliot, M.P. On the first day Professor Hilda Lloyd, President of the Royal College of Obstetricians and Gynaecologists, will deliver the principal lecture, and on the succeeding days other well-known authorities will be speaking.

Renal Association

The third general meeting of the Renal Association will be held at the Ciba Foundation, 41, Portland Place, London, W.1, on Thursday, October 26, at 4.30 p.m. The subject will be "Renal Innervation"; the speakers will be Dr. de Muylder and Dr. El Asfoury. The opening papers will be followed by a discussion. The meeting will be preceded by a demonstration of slides starting at 3 p.m.

British Orthopaedic Association

The annual meeting of the British Orthopaedic Association will be held on October 26–28 under the presidency of Mr. S. L. Higgs at Friends House, Euston Road, London, N.W.1.

Edinburgh Lectures

In connexion with the postgraduate courses in internal medicine and surgery the Edinburgh Postgraduate Board for Medicine has arranged a series of open lectures starting on Friday, October 27, in the Anatomy Lecture Theatre, Edinburgh University, New Buildings. All students and graduates are invited to attend. Details will be published under "Societies and Lectures" in the *Journal*.

Pneumoconiosis Research Unit

The Lord President of the Council, the Rt. Hon. Herbert Morrison, M.P., will open the new laboratories of the Pneumoconiosis Research Unit of the Medical Research Council at Llandough Hospital, near Cardiff, on Saturday, October 28, at 2.45 p.m.

Royal College of Obstetricians and Gynaecologists

A postgraduate course of advanced lectures for those studying the special practice of obstetrics and gynaecology will be held at the Royal College of Obstetricians and Gynaecologists, 58, Queen Anne Street, London, W., the first session on November 3 and 4, and the second session on November 17 and 18. The fees are £3 3s. for the two sessions; £2 2s. for one session; and 10s. 6d. for single lectures. Admission is by ticket only, obtainable from the secretary of the college. Details of the lectures will be published in the "Societies and Lectures" column of the *Journal*.

Westminster Hospital Students' Union

The annual ball of the Westminster Hospital Students' Union will be held at Dorchester Hotel, Park Lane, London, W., on Friday, November 3, with dancing from 9 p.m. until 2 a.m.

Manchester Ball

The Manchester Medical Students' Representative Council is organizing a Winter Medical Ball to be held in the Whitworth Hall of the University of Manchester on Friday, November 10. This function has the support of the Manchester Medical Society and the Medical Board of the Manchester Royal Infirmary. It is hoped that this social occasion will become again an annual feature in the medical life of Manchester. Dancing: 8.30 p.m. to 2 a.m. Buffet: 10 p.m. to 12.30 a.m. Double ticket: one guinea. Further information and tickets may be obtained from the Dance Secretary, the Medical School, Manchester, 13.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

●HUNTERIAN SOCIETY.—At Talbot Restaurant, 64, London Wall, London, E.C., October 23, 7 for 7.30 p.m., dinner meeting. "*A Gastric Gossip*," presidential address by Sir Arthur Porritt.

●INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, London, W.C.—October 23, 5 p.m., "*Poliomyelitis*," by Dr. F. M. R. Walshe.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—October 23, 4.30 p.m., lecture-demonstration for postgraduates by Dr. E. Stengel.

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, Cavendish Square, W.—October 23, 8.30 p.m., "*Pancreatitis*," discussion to be introduced by Professor Ian Aird and Dr. H. T. Howat.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 23, 3.45 p.m., "*General Pathology of the Central Nervous System*," by Professor T. Crawford; 5 p.m., "*Surgical Treatment of Some Types of Urinary Incontinence*," by Dr. Terence Millin.

Tuesday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., October 24, 5.30 p.m., "*Renal Function in Early Life*," by Professor R. A. McCance, F.R.S.

CHADWICK TRUST.—At Westminster Medical School (Sir Edward Meyerstein Lecture Theatre), 17, Horseferry Road, Westminster, London, S.W., October 24, 4.30 p.m., "*Public Health Administration in Western Union Countries: A Comparative Synthesis*," by Dr. Neville M. Goodman (Ministry of Health).

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—October 24, 5 p.m., "*Newer Antibiotics in Dermatology*," by Dr. F. R. Bettley.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—October 24, 5 p.m., "*Genetics in Ophthalmology*," by Professor Arnold Sorsby.

UNIVERSITY COLLEGE, Gower Street, London, W.C.—October 24, 5.15 p.m., "*Some Recent Advances in the Physiology of Vision*," by Professor Hamilton Hartridge, F.R.S.

Wednesday

GLASGOW UNIVERSITY.—In Department of Ophthalmology, October 25, 8 p.m., "*Biological Action of Radiation*," by Dr. J. M. A. Lenihan.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—October 25, 5 p.m., "*Medical Mycology*," lecture-demonstration by Dr. R. W. Riddell.

●INSTITUTE OF PHYSICS: EDUCATION GROUP.—At Fyvie Hall, The Polytechnic, Regent Street, London, W., October 25, 3 p.m., "*Technical Universities*," by Lord Eustace Percy.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 25, 3.45 p.m., "*Anatomy of the Mouth and Pharynx*," by Professor J. Whillis.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—October 25, 5.30 p.m., "*Ophthalmic Neurology*," by Mr. L. H. Savin.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—October 25, 3.30 p.m., "*Modern Methods of Refuse Disposal*" (illustrated), by Mr. H. Ardern, A.M.I.Mech.E., F.Inst.P.C.

SOCIETY OF CHEMICAL INDUSTRY: FOOD GROUP: NUTRITION PANEL.—At Chemical Society's rooms, Burlington House, Piccadilly, London, W., October 25, 6.15 p.m., "*Factors in Distribution Affecting the Quality and Nutritional Value of Foodstuffs: Fish and Meat*." Speakers, Drs. G. A. Reay, E. H. Callow, and M. A. Pyke.

Thursday

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, Cavendish Square, London, W., October 26, 8 p.m., "*The Influence of Adlerian Principles on Modern Psychiatry*," by Professor R. Dreikurs (Chicago Medical School). Discussion to be opened by Drs. E. B. Strauss and E. Weissmann.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., October 26, 5.30 p.m., "*Experimental Research in Chemotherapy*," by Sir Charles Harington, Ph.D., F.R.S.

HONYMAN GILLESPIE LECTURE.—At University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh, October 26, 5 p.m., "*Filariasis*," by Dr. John M. Bowie.

MEDICO-LEGAL SOCIETY.—At 26, Portland Place, London, W., October 26, 8.15 p.m., "*Doctors and the Law*," by Rt. Hon. Sir Travers Humphreys.

ROYAL ARMY MEDICAL COLLEGE.—At Lecture Theatre, John Islip Street, London, S.W., October 26, 5 p.m., "*The Maintenance of Fluid Balance*," by Dr. H. L. Marriott.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 26, 3.45 p.m., "*Arteries and Veins*," by Professor H. A. Harris.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—October 26, 5.30 p.m., "*Visual Fields: Normal and Pathological*," by Mr. C. Taylor.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—October 26, 4.30 p.m., lecture-demonstration on psychiatry by Dr. M. A. Partridge.

TORQUAY AND DISTRICT MEDICAL SOCIETY.—October 26 (1) at Torbay Hospital, 4.30 p.m., "*Tuberculous Lymphadenitis*," by Sir James Paterson Ross; (2) at Palace Hotel, Torquay, 7.30 for 8 p.m., dinner and dance.

WINGFIELD-MORRIS ORTHOPAEDIC HOSPITAL: NUFFIELD ORTHOPAEDIC CENTRE, Oxford.—October 26, 8.30 p.m., "*Personal Experience of Tuberculosis of Hip*," by Mr. J. Agerholm.

Friday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, October 27, 5 p.m., "*Some Aspects of Heart Surgery*," by Mr. R. C. Brock.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, London, W.C.—October 27, 4.30 p.m., "*Otitic Barotrauma*," by Air Commodore E. D. D. Dickson.

KENT AND CANTERBURY HOSPITAL, Canterbury.—October 27, 5 p.m., clinical meeting.

MAIDA VALE HOSPITAL MEDICAL SCHOOL, London, W.—October 27, 5 p.m., clinical neurological demonstration by Dr. W. Russell Brain, F.R.C.P.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, London, W.—October 27, 8 p.m., "*A Survey of Radiological Changes Encountered in Venereal Disease*," by Dr. K. H. Gaskell. A discussion will follow.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 27, 5 p.m., "*Surgical Aspects of Tabes Dorsalis*," by Dr. R. Lees.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—October 27, 4.30 p.m., "*Medical Ophthalmology*," by Mr. A. J. Cameron.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—October 27, 8 p.m., "*The Surgery of the Heart*," address by Mr. R. C. Brock.

APPOINTMENTS

CROYDON GROUP HOSPITAL MANAGEMENT COMMITTEE.—*General Hospital:* J. C. Tainsh, M.B., Ch.B., D.R., Full-time Radiologist, and to carry out part-time duties at Purley and District War Memorial Hospital: L. R. Spencer, M.B., B.Chir., Casualty Officer. *Mayday Hospital:* S. Oram, M.D., F.R.C.P., Cardiologist, with sessions at Mayday and General Hospitals.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—*Senior Casualty Physician* (*Senior Registrar Grade*), D. J. Conway, M.D., D.C.H., D.T.M.&H. *Assistant Radiologist* (*Senior Hospital Medical Officer*), John Sutcliffe, M.B., B.Ch., M.R.C.P., D.M.R.D. *House-physicians* (*Junior Registrar Grade*), L. C. Harris, M.D., M.R.C.P., S. N. Nabarro, M.B., Ch.B., M.R.C.P., R. G. Welch, M.B., B.S., M.R.C.P. *House-surgeon to the Orthopaedic and Plastic Departments* (*Junior Registrar Grade*), D. Duncan, M.B., Ch.B. *Assistant Resident Medical Officer, Tadworth Court* (*Junior Registrar Grade*), M. G. Martin, M.B., Ch.B.

MAW, T. STAFFORD, M.B., Ch.B., D.O.M.S., Senior Registrar, Ophthalmic Department, Royal Victoria Infirmary, Newcastle-upon-Tyne.

RATNER, EDWIN, M.D., D.P.H., Consultant Chest Physician, Oldham and Ashton Area, Manchester Regional Hospital Board.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Cooper.—On October 2, 1950, at Queen Charlotte's Hospital, Hammersmith, to Frieda (formerly Bell), wife of Dr. J. R. Cooper, a daughter—Monica Frieda.

Fallon.—On October 7, 1950, at Royal Infirmary, Edinburgh, to Hazel (formerly Spink), wife of Martin Fallon, O.B.E., M.Ch., F.R.C.S.I., a son.

Gwynne Williams.—On October 5, 1950, at The Infirmary, Denbigh, to Peg, the wife of Dr. T. Gwynne Williams, a brother for Ann.

May.—On September 13, 1950, at Newbury House Nursing Home, to Sylvia, wife of Surgeon Lieutenant C. R. May, R.N., a son—Nigel.

Morrison.—On October 8, 1950, at Bankhall Hospital, Burnley, to Dr. Agnes, wife of Dr. A. B. Morrison, a son.

MARRIAGES

Mathers—Mould.—On September 16, 1950, at Stroud, George Crosthwaite Mathers, M.B., D.R.C.O.G., of Lezayre, Whitehaven Road, Workington, Cumberland, to Diana Mary Mould, S.R.N., of Rowcroft House, Stroud, Gloucestershire.

DEATHS

Binns.—On October 12, 1950, at Little Holland, Ludham, Norfolk, John Braybrooke Binns, M.R.C.S., L.R.C.P.

McIntyre.—On October 7, 1950, at the Kent and Sussex Hospital, Tunbridge Wells, Sir John McIntyre, K.B.E., C.B., M.C., M.B., B.Ch., Air Vice-Marshal, R.A.F., retired.

Rowling.—On October 12, 1950, at 15, Blenheim Terrace, Leeds, Samuel Thompson Rowling, M.D., D.A.

Scoresby-Jackson.—On October 3, 1950, at East Hill Lodge, Dunsford, Exeter, Thomas Scoresby-Jackson, M.B., Ch.B., D.P.H.

Simmons.—On October 8, 1950, at Monxton, Andover, Hants, Stewart Septimus Simmons, M.R.C.S., L.R.C.P., late of South Norwood, London, S.E., aged 80.

Tait.—On October 9, 1950, at the Royal Infirmary, Edinburgh, Robert Horsburgh Tait, M.D., D.P.H., of 55, Argyle Crescent, Portobello, Midlothian.

Thomson.—On October 3, 1950, at 1, Newlands Road, Horsham, Sussex, William Thomson, M.B., C.M., late of Waltham Abbey, Essex.

Webber.—On October 4, 1950, at Headington Hospital, Oxford, Henry Woolmington Webber, M.D., M.S., F.R.C.S.Ed.

White.—On October 11, 1950, at the Royal Infirmary, Edinburgh, James Hunter White, M.B., C.M., aged 81.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Familial Incidence of Mongolism

Q.—*What is known about the mechanism of the inheritance of mongolism? The history of the family with whom I am concerned is as follows:*

Grandmother.—Normal, but with a bad family history of mental and nervous troubles.

First generation.—Two sons and four daughters, the youngest a mongol, the other five normal.

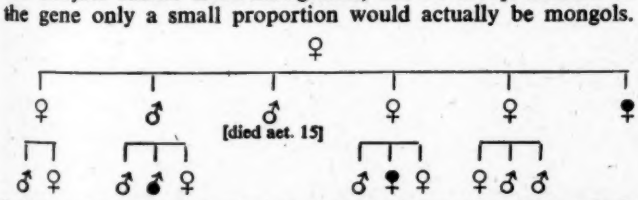
Second generation.—Eldest son: three children, one a mongol. Eldest daughter: two normal children. Second daughter: three children, two normal, one a mongol. Third daughter: three normal children.

The diagnosis in all three cases has been confirmed by experts.

The mothers of the mongol children were respectively aged 44, 40, and 39 when their mongol children were born. The maternal ages at which the unaffected children of the second generation were born were, in order, 35, 37; 38, 43; 34, 42; 31, 33, 38.

What are the probabilities of the normal children of the second generation, when they marry, producing a mongol child? Two mental specialists whom the parents of these children consulted before their marriage told them that mongolism was not inherited—an opinion which does not seem to be borne out by the above facts.

A.—The role of heredity in the production of mongolism is still obscure. A few writers deny that hereditary constitution is involved at all, but this seems too extreme a view. Large collections of data show that amongst the sibs of mongols the occurrence of similar cases is slightly but definitely higher than would be expected by chance, given the incidence of the condition in the general population. Familial incidence, however, is not necessarily a proof of the existence of a genetic mechanism; it might conceivably be due to some non-genetic abnormality in the mother. Much more convincing evidence is the raised incidence amongst more distant relatives of mongols. The practical importance of genetic constitution must be relatively small compared with that of other factors. One could imagine a dominant gene whose possession is necessary before the subject suffers from mongolism, but of the possessors of the gene only a small proportion would actually be mongols.



Pedigree drawn from particulars given in the question: the mongol children are shown in black.

The only other aetiological factor identified with certainty is the age of the mother; the incidence of mongolism rather more than doubles with each advance of five years after the age of 25, and in the oldest age groups may reach quite a high figure.

The pedigree described in the question is highly unusual. The specialists who were consulted were perfectly correct in advising that the risk was negligible that the brothers and sisters of a mongol might themselves have mongol children. The experience in this family does emphasize, however, that it is wise to guard oneself by explaining that the risk, though very small indeed, is nevertheless somewhat greater than for the ordinary person with no close mongol relative. In spite of what has happened the chances for the children of the normal persons of the last generation are probably still good and the risk, though definitely increased as against the chance of 1 in 700 or so that any random pregnancy will end with a mongol child, is likely to be quite small. In all probability it is less likely that one of these persons having a child when the mother is 25 will produce a mongol than that any random woman of 40 or over will do so.

Fibrocystic Disease of the Pancreas

Q.—*The first and third children of a healthy woman have fibrocystic disease of the pancreas. What are the chances of further children being affected?*

A.—The evidence has now become very strong that fibrocystic disease of the pancreas is due to a recessive gene. At all events once the condition has appeared in a sibship the empirical chance of any subsequent child being affected is close to the theoretical figure of one-quarter. Should this mother become pregnant again, the chance is one in four that the child will suffer from the disease.

Prefrontal Leucotomy

Q.—*(a) What are the indications for prefrontal leucotomy, and what is the prognosis? (b) Has the operation been used to alleviate craving in drug addiction?*

A.—*(a)* Prefrontal leucotomy is a symptomatic treatment used in a wide variety of conditions ranging from major forms of insanity, through chronic neurotic illnesses involving tension and distress of mind, to the states of demoralization that can be induced even in normal personalities by intractable pain. It is therefore impossible to state the operative indications succinctly, but (1) the patient should be severely incapacitated before the operation is contemplated, (2) other appropriate treatments, if any, should have been tried, and (3) the best results occur in conditions specially characterized by emotional excess in the form of agitation with tension and distress. The outcome depends on the nature, severity, and duration of the underlying condition, and on the personality of the patient. The better the patient's personality the better is the outcome likely to be. At best after the operation the patient may be a normal person without appreciable handicaps. But where the pre-operative condition has become so fixedly established as to show variation neither spontaneously nor in relation to circumstances, it will persist after operation, though usually in a modified and less distressing form so that the symptoms will be more easily tolerated. It is advisable to seek a second, and preferably expert, opinion before recommending the operation, and in the present state of our knowledge the prognosis should be guarded rather than confident.

(b) Yes, with variable results. The prevailing opinion is that there is some hope of success where the addiction has been more rather than less symptomatic in the sense that it has arisen from attempts to meet undue stress (whether psychic, as in drinking to alleviate depression, or somatic for intractable pain). The less obvious the cause and the less excuse for the addiction, the less good are the operative results. Indeed, where a personality is essentially an unsatisfactory one and the patient has taken to drugs apparently for little reason, the post-operative state is, if anything, liable to be worse, since the post-operative reduction of worry and of restraint is liable to encourage the search for even more immediate gratification of the desires. On the other hand, where drug addiction has arisen more excusably from intolerable pain or even in the hope of quieting a genuine psychic turbulence, the outlook is more hopeful. Quite a number of addicts subject to intolerable pain have been enabled to dispense with drugs altogether after this operation, and so have a few who drifted into the habit through genuine psychic stress.

The Hymen

Q.—*What is the origin of the human hymen?*

A.—The hymen is functional only in female mammals possessing a urogenital sinus (such as the sow), and in these it constitutes a barrier to the flow of urine into the vagina. The human female has no urogenital sinus, but the hymen persists, just as the male nipple persists, because it is part of the hereditary make-up of the mammalian body.

Anoxia and Liver Damage

Q.—*Is it true that the anoxia accompanying severe anaemia can cause liver damage?*

A.—It is important not to confuse anoxic anoxia—i.e., anoxia associated with low oxygen tension—with that due to anaemia, in which the oxygen tension is usually normal. The former cannot be compensated by an increased blood flow, whereas in the latter increased cardiac output may largely make good the deficiency. That anoxic anoxia may lead to liver damage has been undoubtedly established both in men and animals (Buchner, H., *Klin. Wschr.*, 1942, **21**, 721), severe cases resulting in extensive centrilobular necrosis. Uncomplicated anaemia, however, does not generally lead to necrosis: the more usual finding is some degree of fatty infiltration, as, for example, in inadequately treated cases of pernicious anaemia. On the other hand, a degree of circulatory impairment which might be innocuous in a subject with a normal haemoglobin level may well lead to anoxic liver damage in a severely anaemic subject whose liver cells have been dependent for adequate oxygenation upon an increased blood flow. Any increased metabolic activity of the liver in these circumstances may also upset the balance between supply and demand. Such an increased demand may well result from the metabolic disturbance engendered by major surgery and its accompanying anaesthetizing agents.

Vitamin D and Bronchitis

Q.—*An otherwise healthy boy of 9 years living under first-class conditions suffers from recurrent attacks of bronchitis during the winter. Would vitamin D be beneficial and, if so, has an ultra-violet lamp any advantages over direct administration? What, besides burns, are the dangers of such a lamp?*

A.—Scientifically conducted experiments with groups of children in Great Britain have so far failed to show that ultra-violet light externally or vitamin administration has any beneficial effect in reducing the incidence of respiratory tract infections. This does not exclude the possibility of an individual child receiving some benefit, but it makes it unlikely. The main danger of ultra-violet light, apart from burns, is the well-recognized risk of lighting up a tuberculous infection in the lungs—an unlikely event, however, in a boy of 9. There is also the point that the warming of the skin which occurs, if followed by exposure to colder conditions, may be succeeded by the sort of "chilling" which seems to precede some of the respiratory tract infections.

It may be permitted to follow this largely negative answer with some comments on the condition described. There are three possibilities which might be usefully considered: First, where is the infection coming from? If the child is "otherwise healthy" the question of infection from some other member of the household should be investigated. A sinus infection, a throat infection in mother or father with whom the children are living so to speak in symbiosis may spread to a child. Does the term "otherwise healthy" exclude the chance that the child has infection of an antrum, of the tonsils, or even a small area of collapsed and infected lung only to be recognized on *x*-ray examination? Secondly, has the possibility of allergy been excluded? Some cases of recurrent bronchitis in the young are in effect really asthma. Thirdly, it is fair to ask what the "first-class conditions" really mean. Overheated rooms, lack of fresh air, too many clothes, lack of exercise, or absence of precautions to keep warm after exercise may all occur at the best economic levels. Over-protection may result in lack of immunity.

Bleeding Gums

Q.—*An otherwise healthy man suffers from bleeding gums. Every morning his teeth and gums are covered with a brown nasty smelling deposit. What is the best treatment?*

A.—There are numerous forms of gingivitis due to many causes, and any treatment prescribed without investigation of possible causes is bound to be empirical. In general, local scaling and cleaning are indicated to keep the teeth clean and polished, thereby preventing food sticking to them, with finger-massage to restore tone in the gums. If the pockets round the teeth are deep, gingivectomy—i.e., trimming away superfluous and swollen gums—may be undertaken. Local penicillin in the mouth is of use in acute cases, but it is not much good in long-standing cases.

Treatment of Leucopenia

Q.—*A woman aged 55 has been taking "tridione" for several months for petit mal. In four months her total leucocyte count has fallen from 5,000 per c.mm. to 3,500 per c.mm. The tridione has now been stopped. What other measures should be adopted to increase the number of leucocytes to normal?*

A.—It is questionable whether a fall of the total leucocytes from 5,000 per c.mm. to 3,500 per c.mm. is of any significance, unless repeated counts showed the second figure to be constant. The range for 95% of normal individuals is 4,000-11,000 per c.mm.; thus it is possible that the count of 3,500 is a solitary low reading. If it is established that there is persistent leucopenia, tridione should be stopped and the patient kept under observation. The count will almost certainly rise spontaneously after withdrawal of the toxic agent. Folic acid, pyridoxine, and crude liver extract have all been thought at one time or another to stimulate leucopoiesis; it is more than doubtful whether they exert any such action, but they are worth a trial. There is, in fact, no drug known which increases the formation of leucocytes. The most important part of treatment is the immediate control of any infection should evidence of such occur.

NOTES AND COMMENTS

Splenomegaly in Thrombocytopenic Purpura.—Dr. Bernard Myers (London) writes: In your reply ("Any Questions?" September 30, p. 793) you state that "palpable enlargement of the spleen occurs in about one-third of patients with primary or idiopathic thrombocytopenic purpura." In a series of cases which Mr. Rodney Maingot and I had together which from the tests and clinical observation were essential thrombocytopenic purpura, there was not a single case, clinically or at the operation of splenectomy, in which the spleen was in any degree enlarged. I found when I made this statement to medical societies in the United States that the same was the experience of the profession there.

"Hospital Improvements."—This booklet by Miss Olive Matthews, which was referred to in an annotation last week (p. 878), is obtainable only from the author at 22, Harrington Gardens, London, S.W.7 (1s. 6d., post free).

Correction.—Dr. Byron E. Hall (Rochester, Minnesota, U.S.A.) writes: In the *British Medical Journal* of September 9 (p. 585) a paper bearing the title "Studies on the Nature of the Intrinsic Factor of Castle" was published with my name as sole author. When the manuscript was submitted to Professor Justin Besançon, secretary-general for the First International Congress of Internal Medicine, last July, I was not cognizant of the fact that it would be published, especially prior to the meeting of the Congress. The manuscript was incomplete to the extent that the names of associates who had worked with me on this project and acknowledgments to certain pharmaceutical firms had been omitted. Dr. E. H. Morgan, formerly a fellow in medicine, Mayo Foundation, and Dr. D. C. Campbell, consultant in medicine, Mayo Clinic, should have been co-authors. Moreover, acknowledgments to Merck and Company, Rahway, New Jersey, for supplying crystalline vitamin B_{12}; to the Abbott Laboratories, North Chicago, Illinois, for extracts of hog gastric mucosa; and to the Upjohn Company, Kalamazoo, Michigan, for vitamin B_{12} concentrate and extracts of hog duodenum should have been included.

All communications with regard to editorial business should be addressed to The EDITOR, British Medical Journal, B.M.A. House, Tavistock Square, London, W.C.1. Telephone: EUSTON 2111. Telegrams: *Alliology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). Telephone: EUSTON 2111. Telegrams: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. Telephone: EUSTON 2111. Telegrams: *Medisecra, Westcent, London.*

B.M.A. Scottish Office: 7, Drumsheugh Gardens, Edinburgh.